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CADMIUM

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and Gunnar Nordberg, M.B.
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A review on cadmium is presented which focuses on information essential to the understanding of the toxic action of cadmium and the relationship between dose (exposure) and effects on human beings and animals. The following areas are covered in this presentation: Occurrence of cadmium - possible routes of exposure and daily intake; metabolism of cadmium; respiratory effects and dose-response relationships; systemic effects and dose-response relationships; carcinogenic and genetic effects; the Itai-Itai disease. (APTD)

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CHAPTER 1

INTRODUCTION

This review on cadmium in the environment has been performed under a contract between the U.S. Environmental Protection Agency and the Department of Environmental Hygiene of the Karolinska Institute, Sweden. The Project Officer of the Air Pollution Control Office of the U.S. Environmental Protection Agency has been Robert J. M. Horton, M.D.

The focus of the report is upon information essential to the understanding of the toxic action of cadmium and the relationship between dose (exposure) and effects on human beings and animals. The therapy of cadmium poisoning has not been discussed.

The report is intended to serve as a background paper for a future Air Quality Criteria document on cadmium. Therefore, particular attention has been given to information relevant for the evaluation of risks due to long-term exposure to low concentrations of cadmium. Acute effects from short-term exposure to high concentrations are dealt with briefly. In vitro studies without bearing on the main problem have not been dealt with.

The report is not limited to effects from exposure via inhalation. Newly accessible information, showing that large populations may be exposed considerably via the oral route, can elucidate chronic effects of cadmium in general. Man and animals can be victims of secondary exposure through vehicles such as food and water which have been contaminated by cadmium in air.

Cadmium is in the air as an aerosol. Hitherto only inorganic cadmium compounds have been found in nature and there are no data available on the toxicity of organic compounds. This review deals only with inorganic cadmium compounds.

Although data presented are based mainly on a literature survey and on our own experience, we wish to express our deep appreciation for the additional information made available to us through correspondence with and personal visits to scientists in several countries. Most of the information from Japan would not have been possible to evaluate and include in this report, had we not had the advantage of a most generous collaboration with the Japanese Ministry of Health and Welfare, the Prefectural Departments of Public Health in Toyama, Nagasaki and Gumma, the Japanese Association of Public Health, industries, particularly the Kamioka Mine of the Mitsui Mining and Smelting Company, as well as independent researchers in Japan. We wish to express our gratitude especially to Drs. Michio Hashimoto, M.D. and Yoshima Yamamoto, M.D., former and present chiefs, respectively, of Environmental Pollution Control Section, Bureau of Environmental Sanitation, Ministry of Health and Welfare, and to Kenzaburo Tsuchiya, M.D., Professor of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan.

We express our thanks to Miss Pamela Boston for assistance in editing the English of the report. Part of the expense for a visit to Japan was provided by the Swedish National Environmental Protection Board, the assistance of which is acknowledged.

CHAPTER 2

PROBLEMS OF ANALYSIS

Biological effects of cadmium cannot be discussed without taking into account the analytical methods used. When concentrations of cadmium in air, water, food, body fluids and organs are compared to each other or related to effects, one must be sure that a proper method is being used for the determination of cadmium, otherwise erroneous conclusions may be drawn.

The following properties of an analytical method are of interest:

1) Specificity: The method used must measure only cadmium. If other substances interfere, they must be either eliminated or a correction must be made allowing for their presence.

2) Sensitivity: The minimum amount or concentration that the method will detect.

3) Precision: The error of the method, often expressed as the coefficient of variation, is evaluated by a number of analyses on the same sample over a certain period of time. Precision is often dependent on the concentration.

4) Repeatability: By running duplicates of the samples and by having the deviation of the two values from their mean expressed as a percentage repeatability is obtained.

5) Accuracy: This means the systematic deviation from the true values.

Many methods have been used for the determination of cadmium, but during the last two decades four methods have been dominating, and as it is expected that all four will be used for many years to come, they are being discussed here. These methods are: 1) Colorimetric determination after wet digestion and extraction with dithizone (Dithizone methods); 2) Emission spectroscopy; 3) Neutron activation and 4) Atomic absorption spectrophotometry. These methods have recently been discussed also by Yamagata and Shigematsu, 1970.

2.1 DITHIZONE METHODS

The basic principle is that cadmium forms a stable complex with dithizone at an alkaline pH. The many other metals, that form complexes with dithizone must first be eliminated. Examples of dithizone methods which have been used for the determination of cadmium are the ones by Church, 1947, Saltzman, 1953 and by Smith, Kench and Lane, 1955. With regard to precision etc., there is scarce information in the literature. If proper steps are taken to remove other metals, the method must be regarded as being specific, but, on the other hand, there is always a risk of contamination with cadmium from reagents during all the steps. If blanks and standards are treated exactly in the same way as the samples, this error will be eliminated.

Dithizone methods have been used for the determination of cadmium in urine, where normally only a few micrograms per liter are found, and for the determination of cadmium in foodstuffs and organs. The results obtained by this method seem to compare favorably with results obtained by other methods. (See table 2:1). In the following chapters, the dithizone method will be regarded as a useful method for determination of cadmium in biological material.

2.2 EMISSION SPECTROSCOPY (SPECTROGRAPHY)

The basic principle is that by exciting metal atoms by high energy sparks or electric arcs, the atoms will emit light of a characteristic spectral distribution. The spectral lines may be recorded on a film, which makes it possible to get a qualitative or quantitative estimate of the metals. Tipton et al., 1962, studied the precision for determinations in organs and found that the coefficient of variation was 19 percent at concentrations of 220-3,400 ppm cadmium in the ash. The repeatability varied between 5 and 7 percent for liver and kidney. The sensitivity was 50 ppm cadmium in ash.

Geldmacher-v. Mallinckrodt and Pooth, 1969, have also used a spectroscopic method for the determination of metals, including cadmium, in biological material. After wet ashing, the metals were extracted with diethylammonium-diethyldithiocarbamate in chloroform and after removal of the solvent the analysis was performed. They stated that they could detect 1 μg of cadmium, but made no further studies on the method. Imbus et al., 1963, determined cadmium in urine and blood after extraction with dithizone. The lower limit of sensitivity was 0.1 μg per sample and by using 25 ml of blood or 250 ml of urine, about 0.4 μg could be detected in 100 ml and 1,000 ml respectively.

The sensitivity has been improved during recent years and at present 0.02 μg can be detected in samples with modern equipment, that is, that it is possible to determine 0.2 μg per 100 ml blood, by using 10 ml samples.

It seems that some earlier spectrographic methods have had a relatively low sensitivity and that accurate quantitative determinations of cadmium could only have been obtained in organs with relatively large concentrations, such as liver and kidneys.

2.3 NEUTRON ACTIVATION

The basic principle is that by irradiation of the sample with elementary particles, chiefly neutrons, radioactive nuclides will be obtained. Elements can be identified with the aid of their energies and half-lives. It is often necessary to introduce separation steps by chemical methods. This is a method which should be quite specific for cadmium, but until now neutron activation has only been used in a few investigations on cadmium and the number of determinations has been small (Westermark and Sjöstrand, 1960, Axelsson and Piscator, 1966a, Piscator and Axelsson, 1970, Plantin, 1964, Lieberman and Kramer, 1970, Wester, 1965, Henke, Sachs and Bohn, 1970).

2.4 ATOMIC ABSORPTION SPECTROPHOTOMETRY

The basic principle is that the sample is passed into a high temperature burner, so that the excited atoms will pass through a path of light emitted from a lamp with a cathode of a specific metal. If the sample contains the actual metal, the atoms from that metal will absorb the light and the absorbance can be read on a meter.

At present, atomic absorption is the most commonly used method for the determination of cadmium. The sensitivity is high and concentrations as low as 0.005 ppm can be determined in pure water solutions. There has been a lot of optimism about atomic absorption, but the difficulties have often been overlooked. Pulido, Fuwa and Vallee, 1966, have thoroughly discussed the determination of cadmium in biological material. They studied interference by other substances and found that phosphate in concentrations above 0.1 M could decrease the absorbance and that sodium chloride in concentrations above 0.01 M could increase absorbance. By using a hydrogen lamp, they could allow for the presence of NaCl in serum and urine and obtain more true values. The specificity of cadmium determinations with atomic absorption is thus dependent on the amount of NaCl and other compounds in the sample, but still cadmium in urine and serum has been determined in several investigations without taking the presence of NaCl into account. It should be pointed out that Pulido, Fuwa and Vallee, 1966, found in ten normal urines, a mean value of 0.009 µg per ml urine, which is higher than that reported when extraction methods have been used (see section 4.3.3). It is possible that there are factors hitherto not investigated that might influence the determination of cadmium in, for example, normal urine. Pulido, Fuwa and Vallee, 1961, used a special apparatus giving a very high sensitivity, but with commercially available apparatus, it will not be possible to determine cadmium in urine without a preliminary concentration of cadmium.

If interfering substances are not present, the accuracy is very high. Pulido, Fuwa and Vallee, 1965, reported on two samples with a concentration of 0.165 and 0.051 ppm of cadmium (National Bureau of Standards' sample) where they found an accuracy of 99.4 and 104.5 percent. Repeatability was 2 percent when nine duplicate analyses of cadmium in metallothionein were done. When atomic absorption was compared with emission spectrography, values were obtained from 95-113 percent of those obtained with the latter method.

The difficulties encountered when investigating cadmium in biological materials at a low concentration of cadmium are not found to the same degree when analyzing tissues with a high cadmium content such as kidney and liver. Repeatability was 3.2 percent for determination of cadmium in liver and kidneys as reported by Morgan, 1969, and similar values were found by Piscator for cadmium in renal cortex (unpublished data).

During recent years, it has been recognized that it might be necessary to extract the metals into an organic solvent before analysis. This will give a higher concentration, and interfering salts will be eliminated. One method is to digest the sample with acid, adjust the pH to around 3 and extract it with a chelating agent such as ammoniumpyrrolidine dithiocarbamate (APDC) in methylisobutylketone (MIBK). Such a method for the determination of cadmium in urine and serum has been described by Lehnert, Schaller and Haas, 1968.

In a Japanese report (Japanese Public Health Association, 1970 c) it is seen that most laboratories used first an extraction with dithizone of the digested sample and then once again extracted cadmium with acid before determination with atomic absorption was done. Table 2:1 shows the results from analyses in 6 different laboratories of urines from cadmium exposed workers and patients with Itai-itai disease. There is a good agreement between most of the laboratories.

The latest improvement in cadmium determination is the flameless atomic absorption in a graphite atomizer, which makes it possible to determine about 0.01 ng in 20 μl of urine, according to preliminary results, provided that a deuterium background corrector is used (Linnman and Lind, unpublished data).

2.5 CONCLUSIONS

There are several methods that can be used for the determination of cadmium in biological material, such as blood, urine, organs and food. At present, the most commonly used method is atomic absorption spectrophotometry, but interference from salts, such as NaCl, may give erroneous results especially when low concentrations are determined. Such interference may be avoided by using extraction technics or background correctors.

Except for one Japanese investigation, no collaborative study has been performed by laboratories engaged in research on biological effects of cadmium. Such a study is necessary as this would facilitate comparisons in the future of parameters such as cadmium in food, cadmium in urine or blood.

Table 2:1 CADMIUM CONCENTRATIONS IN 13 URINES (μg/l) DETERMINED IN 6 LABORATORIES. (From Japanese Public Health Association, 1970c).

	1	2		3			4	5	6
		a	b	a	b	c			
1	16.6	41.0	12.7	19.4	14.6	9.2	12	12.3	13.8
2	16.0	47.0	12.4	23.0	18.6	16.8	15	12.0	16.4
3	24.0	0	10.4	12.3	9.3	8.4	7	7.3	7.2
4	12.0	6.8	8.9	12.1	9.3	8.4	7	6.0	7.7
5	16.0	12.0	14.6	28.3	24.8	23.2	18	16.5	21.4
6	190.4	153	150.7	178.0	154.8	147.4	182	152.9	194.8
7	53.4	100	48.1	64.8	51.6	44.2	47	49.9	45.8
8	173.6	125	138.3	143.6	128.3	11.6	148	139.2	126.1
9	68.4	56	55.5	63.1	53.2	43.2	48	36.8	24.6
10	39.4	63	38.9	47.1	35.5	31.6	41	35.6	28.3
11	5.4	50	2.4	7.8	4.5	4.2	6	4.0	4.1
12	128	165	125.8	141.9	108.4	105.3	93	136.7	119.2
13	22	26	18.1	17.6	12.9	11.8	20	13.2	13.6

The following methods were used:

Laboratory 1 : Dithizone method
" 2a: Dithizone - atomic absorption. Perkin Elmer apparatus
" 2b: " " " Hitachi apparatus
" 3a: APDC-MIBK extraction (without ashing) - atomic absorption
" 3b: Dithizone - atomic absorption
" 3c: Dithizone method
" 4 : Dithizone - atomic absorption
" 5 : Dithizone - atomic absorption
" 6 : APDC-MIBK - atomic absorption

CHAPTER 3

CADMIUM: OCCURRENCE, POSSIBLE ROUTES OF EXPOSURE AND DAILY INTAKE

3.1 OCCURRENCE AND POSSIBLE ROUTES OF EXPOSURE

Cadmium is closely related to zinc and will be found wherever zinc is found in nature. The cadmium to zinc ratios will vary. In most minerals and soils ratios of 1:100-1:12,000 have been found (Bowen, 1966, and Schroeder et al., 1967). Zinc is an essential metal for most life-forms (Underwood, 1962, Bowen, 1966, Schroeder, 1967 and Yamagata and Shigematsu, 1970). Thus it is probable that no naturally occurring material will be completely free from cadmium.

Cadmium is obtained as a by-product in the refining of zinc and other metals. However, as it is difficult to separate zinc and cadmium, the latter will often be found in small amounts in commercially available zinc compounds, as pointed out by Schroeder et al., 1967.

Though cadmium has been recognized for only a relatively short period of time, copper, lead, zinc and some other metals have been used for several thousand years. Thus, as soon as man started to produce metals, he also started to pollute the environment with cadmium. In this century cadmium and cadmium compounds have been used increasingly by industries, causing a sharp increase in environmental contamination. Cadmium will be emitted to air and water by mines, by metal smelters, especially lead, copper and zinc smelters and by industries using cadmium in alkaline accumulators, alloys, paints, and plastics. The burning of oil and waste in scrap metal treatment will also contribute. The use in agriculture of fertilizers, either as chemicals or as sludge from sewage plants and the use of cadmium-containing pesticides might also contribute to the contamination.

Some of the cadmium emitted to the air will be inhaled by people and animals, but most of it will be deposited in soil or water. The cadmium deposited in water may then increase the concentrations of cadmium in edible water organisms. In the event of flooding or irrigation, cadmium in water might also increase the concentrations in soil, in turn causing an increase of cadmium in agricultural products, such as rice and wheat. However, very little is known about the transfer of cadmium from deposits in soil or water to microorganisms or plants and very little is known about the forms in which cadmium exists. It has been suspected that organic cadmium compounds could exist similar to the ones described for mercury, but it has not been possible to prove the existence of such compounds (Westermark, personal communication).

3.1.1 Cadmium in air

During the last decades, yearly determinations of cadmium in air have been performed in several areas in the United States (Air Quality Data, 1966). Since the analytical methods were not always sensitive enough, some cities in the U.S. have been recorded as having zero levels of cadmium in air. The highest yearly mean concentrations in 1964 were found in Covington, Kentucky, where an average level of 0.05 $\mu g/m^3$ was recorded. The highest quarterly average level in the 3rd quarter in 1964, also found in Covington, Kentucky, was 0.11μg/m^3. Kneip et al., 1970, made daily determinations for one year at several sites in New York City and surrounding areas. They found that lower Manhattan had a yearly mean level of 0.023 μg/m^3, whereas a non-urban site had 0.003 μg/m^3. In Sweden weekly means of 0.3 μg/m^3 were recorded on several occasions 500 meters from a factory using copper cadmium alloys. At a distance of 100 meters from the source, a monthly mean value of 0.6 μg/m^3 was recorded. The highest concentration found in a 24-hour sampling was 5.4 μg/m^3. In the center of Stockholm, weekly means of 0.005 μg/m^3 were found, whereas in a rural area far from cadmium-emitting factories, a monthly mean of 0.0009 μ/m^3 was found (Piscator, unpublished data). In Erlangen, West Germany, Essing et al., 1969, found a level of 0.0015 μg/m^3 (sampling time not stated). In Japan weekly means of 0.5 μg/m^3 (based on 8-hour sampling periods) have been reported at a distance of 100 meters from a zinc smelter. At a distance of 400 meters, the mean levels recorded were 0.2 μg/m^3 (Hasegawa, Ministry of Health and Welfare, personal communication). Near another smelter, 8-hour values of 0.16-0.32 μg/m^3 were obtained at a distance of 500 meters from the source (Kitamura, personal communication).

It thus seems that in areas around cadmium-emitting factories, cadmium concentrations in air several hundred times greater than those in non-contaminated areas will be found.

Monthly deposition of cadmium has been measured around some factories. The results from the years 1968-1970 at locations near a Swedish factory are shown in table 3:1 (Olofsson, 1970). It should be noted that a considerable deposition was sometimes even found at 10 kilometers from the source. Deposition measurements near a Japanese factory during a period of six months showed a mean value of 6.2 mg/m^2/month at a distance of 500 meters from the source and a mean value of 1.8 mg/m^2/month at a distance of 1,400 meters, whereas in two control areas in two cities, values of 0.1 and 0.4 mg/m^2/month, respectively, were found (Kitamura, personal communication). In the United States, Hunt et al., 1970, determined cadmium in dustfall in residential, commercial and industrial areas in 77 cities and found monthly means of 0.040, 0.063 and 0.075 mg/m^2 in the respective areas.

Deposited cadmium has been measured by determining cadmium in mosses (Rühling, 1969, Rühling and Tyler, 1970 and Olofsson, 1970). Figure 3:1 shows how the spreading of cadmium around a factory producing copper cadmium alloys can be determined by this technique. According to Rühling and Tyler, concentrations of cadmium in moss in the more heavily industrialized and more densely populated south of Sweden were between 0.5-1 ppm (dry weight) whereas in the north, they were less than 0.2 ppm. The spread of cadmium from a cadmium-emitting factory can also be studied by determining cadmium in leaves from shrubs, as shown in figure 3:2. These data are from an investigation by Kobayashi et al., 1969, (quoted by Yamagata and Shigematsu, 1970).

The influence of cadmium emissions upon cadmium concentrations in soil has been studied by Kitamura (personal communication). Test pots containing soil were placed 500 meters from the emission source and in a control area. The results are shown in table 3:2. Within a few years, a ten-fold increase in the cadmium concentration occurred in the soil placed near the emission source. At that same location, deposited cadmium was measured as 6.2 mg/m^2/month during a six-month period.

It is important to know the state in which cadmium exists in air, but at present, no data concerning this question are available. Even if it can be presumed that cadmium oxides will constitute a large part of the airborne cadmium, the possibility that other compounds are formed can not be excluded. Particle size is also essential for calculating deposition and absorption in the lungs, but only one report has supplied such information. In Cincinnati, Ohio, cadmium concentrations in the air and mass median diameters of the particles were measured downtown and in a suburb (Lee, Patterson and Wagman, 1968). Concentrations averaged 0.08 and 0.02 $\mu g/m^3$, respectively and MMD averaged 3.1 and 10 microns, respectively. In both areas about 40 percent of the particles were below 2 microns.

3.1.2 Cadmium in water

In areas not known to be polluted by cadmium, values of less than 1 ppb have been reported in water. Values exceeding 10 ppb have been recorded both in natural waters and in water for consumption. Increased amounts of cadmium can be due to the contamination of the water either by industrial discharges or by the metal or plastic pipes used in distribution (Schroeder et al., 1967).

Yamagata and Shigematsu, 1970, have pointed out that in rivers polluted by cadmium, the metal will often be undetectable in the water phase while large concentrations will be found in suspended particles and in the bottom sediments. This is especially true at neutral or alkaline pH. A similar finding was obtained in Sweden, where 500 meters downstream from a cadmium-emitting factory 4 ppb of cadmium were found in water, while 80 ppm (dry weight) were found in the mud (Piscator, unpublished data). To avoid errors when determining the degree of contamination in water, cadmium in the suspended particles or the sediments must be measured. The contamination of rice fields surrounding the Jintsu River, the area in Japan where the Itai-itai disease has occurred, is probably due to the transport of cadmium-containing suspended particles to the paddy soil by irrigation with river water (Yamagata and Shigematsu, 1970).

3.1.3. Cadmium in soil

It has already been mentioned that both airborne and waterborne cadmium can cause increased concentrations of cadmium in soil. In areas not known to be polluted, the cadmium concentrations in soil have been reported to be less than 1 ppm, with great variations (Schroeder et al., 1967and Yamagata and Shigematsu, 1970). In Japan levels of 1-50 ppm have been found in rice fields in areas under observation for suspected contamination from cadmium (Hasegawa, personal communication, Yamagata and Shigematsu, 1970).

There are other ways by which soil can be contaminated with cadmium. Odén (personal communication) has found high concentrations of cadmium in sludge from sewage treatment plants in Sweden. The use of this sludge as fertilizers could increase cadmium concentrations in soil. Superphosphate fertilizers also contain relatively large amounts of cadmium, as pointed out by Schroeder and Balassa, 1963, and Schroeder et al., 1967).

Information is lacking on what factors determine the uptake of cadmium by plants and on the extent to which selective mechanisms will operate. It is conceivable that such factors as pH and concentrations of other metals will influence the uptake. Two important foodstuffs, rice and wheat, are able to take up considerable quantities of cadmium from soil. Kobayashi et al., 1969, (qouted by Yamagata and Shigematsu, 1970) added cadmium oxide to soil in pots where rice and wheat were growing. The results are shown in table 3:3. It is noteworthy that wheat grains accumulated more cadmium than rice. It can also be noted that concentrations above 10 ppm in soil brought about less yield of both rice and wheat.

3.1.4 Cadmium in food

During later years several investigations concerning the cadmium content of common foodstuffs have been performed (United States: x/ Schroeder et al., 1967; West Germany: Kropf and Geldmacher v. Mallinckrodt, 1968, and Essing et al., 1969; Czechoslovakia: Lener and Bibr, 1970; Roumania: Rautu and Sporn, 1970; Japan: Ishizaki, Fukushima and Sakamoto, 1970a). In table 3:4, some basic foodstuffs are compared. It will be seen that these reports indicate that "normal" levels of cadmium in food are below 0.05 ppm. In the table, only the U.S. values reported by Schroeder and Balassa, 1961, have been included. The data by Schroeder et al., 1967, have been excluded because in the investigation reported in 1967 atomic absorption spectrophotometry was used without any preliminary extraction. For example, cadmium levels in milk were reported to be 0.1-0.4 ppm. Interference from sodium chloride might have been the cause. In the reports quoted it will also be seen that certain foodstuffs may contain higher concentrations of cadmium.

Some seafood, especially shellfish and cuttlefish, has been reported to contain above 0.05 ppm (Schroeder and Balassa, 1961, and Schroeder et al., 1967, and Ishizaki, Fukushima and Sakamoto, 1970a). Such concentrations seem to occur in areas not known to be polluted while much higher concentrations have been reported in areas known to be polluted. Ishizaki, Fukushima and Sakamoto, 1970a, reported values of 10-110 and 92-420 ppm, wet weight, in livers of cuttlefish and shellfish (see also section 8.4.1.12). Pringle et al., 1968, reported that cadmium concentrations varied from 0.1-7.8 ppm, wet weight, in oysters from the east coast of the United States and from 0.2-2.1 ppm

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x/ Schroeder and Balassa 1961,

in oysters from the west coast. Rice and wheat from most parts of the world contain less than 0.1 ppm, but rice and wheat from contaminated areas in Japan have been shown to contain considerably higher concentrations, around 1 ppm (see sections 8.4.1.12 and 8.4.2.1.2) It is not always clear whether Japanese data on rice and wheat refer to wet or dry weight. However, this distinction is of minor importance, as the difference will be only about 10 percent. Liver and kidney, such as from calves or swine, often contain more than 0.05 ppm, whereas meat usually contains less than 0.05 ppm of cadmium. An exception seems to be whale meat, as Ishizaki, Fukushima and Sakamoto, 1970a, reported levels of 0.25 and 0.4 ppm in two samples.

3.1.5 Cadmium in cigarettes

That smoking might be a source of exposure to cadmium has been recognized the last years. Szadkowski et al., 1969, found a mean content of 1.4 µg per cigarette when they determined the cadmium content of 8 cigarette brands in West Germany. Cigarettes were smoked in a smoking apparatus with the following experimental parameters: two puffs a minute, each of two seconds duration, suction volume, 30 ml with a pressure of 80-120 mm H_2O. The mainstream smoke particles were collected on a Cambridge-filter and the gases in nitric acid. They found a mean value of 0.15 µg cadmium per cigarette in the particle phase of the 8 brands and 0.03 µg in the gaseous phase. From their data it can also be seen that about 0.5 µg went into the side stream smoke, i.e., about 35 percent.

Nandi et al., 1969, investigated six different brands of cigarettes. The mean total content was about 1.2 µg per cigarette. They also used a smoking machine, but the experimental conditions were not described in detail. Intermittent suction was used 5 seconds every minute to make the cigarette burn. The smoke was not collected on filters. Cadmium was only determined in the ashes and the filters of the cigarettes. With the method used, they found that about 30 percent of cadmium was recovered in ash and filter and they calculated that about 70 percent passed with the smoke. As they did not separate mainstream and side stream smoke, it can not be known how much cadmium was in the mainstream.

Linnman and Lind (to be published) studied the influence of different numbers of puffs per cigarette and different numbers of puffs per minute in one brand of cigarettes. They used a duration of 2 seconds per puff, a suction volume of 35 ml. They found that one puff per minute and 10 puffs altogether resulted in a collection of 0.14 µg cadmium per cigarette on a Cambridge filter. Two puffs per minute and 15 puffs altogether resulted in 0.19 µg per cigarette on the filter. The same result was obtained with 3 puffs per minute and 15 puffs altogether. The difference between the first value and the second and third ones was statistically significant. These data agree well with the above mentioned findings of Szadkowski et al., 1969, showing that 0.1-0.2 µg of cadmium might be inhaled by smoking one cigarette. Smoking habits will to some extent affect the amount of cadmium in the mainstreams, as shown by the influence of puff intervals on the cadmium amounts.

Piscator and Rylander (unpublished data) exposed guinea pigs to free cigarette smoke for one month (1 cigarette per day for one week, 4 cigarettes per day for 3 weeks). The method used was the one by Rylander, 1969. By means of a suction device, the animals were exposed for two seconds every minute to the smoke from a puff of two seconds' duration. About 10 puffs from each cigarette were given. In table 3:5 the concentrations of cadmium and zinc in the renal cortex of exposed animals compared with controls are shown. The cadmium concentrations are significantly higher in the exposed animals than in the controls. There is also a difference in zinc concentrations.

3.2 DAILY INTAKE OF CADMIUM

Estimates of the daily intake of cadmium based mainly on the data on cadmium concentrations in food have been made in several countries, as shown in table 3:6, together with results from investigations in which an aliquot from the total 24-hour diet has been examined (Tipton and Stewart, 1970, and Boström and Wester, 1968). There is a marked discrepancy when the results of Schroeder et al., 1967, and Tipton and Stewart, 1970, are compared with those of the other investigators. It should be noted that atomic absorption without extraction of the metal was used in these two investigations. As has been pointed out in Chapter 2, there is a risk of obtaining values that are too high with this particular method because of interference from sodium chloride. It should also be noted that in non-polluted areas in Japan, the intake of cadmium does not seem to differ markedly from the intake in the European countries included.

At concentrations below 10 ppb, cadmium in water will contribute very little to the daily intake. A concentration in drinking water around 20 ppb would increase the daily intake with 20-40 μg at a consumption of 1-2 liters per day.

Cadmium in air will also contribute very little in non-polluted areas. If it is assumed that normally around 20 m^3 of air are inhaled every day, concentrations of 0.001-0.01 $\mu g/m^3$ would not give more than 0.02-0.2 μg per day via the respiratory route. The deposited amount would be less than that. It has been mentioned that concentrations of 0.1-0.5 $\mu g/m^3$ have been found around cadmium-emitting factories. These concentrations would cause an inhalation of 2-10 µg per day. This is still less than the oral intake, but as will be discussed in the next chapter, the absorption rates for the gastrointestinal route and the respiratory route are quite different. Thus, exposure via air can be an important factor.

An additional source might be smoking. Twenty cigarettes per day will probably cause the inhalation of 2-4 µg.

It should also be pointed out that there is a possibility of respiratory exposure to cadmium in areas contaminated by cadmium when in dry seasons deposited dust is again tranferred to the air by whirlwinds, etc. Sporting areas and playgrounds for children could be sources of this type of exposure.

3.3 CONCLUSIONS

Human beings will be exposed to cadmium via food, water and air. Exposure via food is the most important. In uncontaminated areas most foodstuffs will contain less than 0.05 ppm of cadmium, wet weight, and the daily intake will be about 50 µg. Liver and kidney from animals and shellfish are among foodstuffs that may have concentrations larger than 0.05 ppm, even under normal circumstances. When certain foodstuffs are contaminated by cadmium in soil and water, the cadmium concentrations may increase considerably. Among these are rice and wheat, in which concentrations around 1 ppm have been reported. This may result in increases in daily intake of cadmium.

In water the normal concentration of cadmium is less than 1 ppb. If the cadmium concentration in drinking water exceeds 10 ppb, it might contribute significantly to the daily intake of cadmium.

Whereas the "normal" concentrations of cadmium in air, about 0.001 µg/m^3, will not contribute significantly to the daily intake of cadmium, in areas where cadmium-emitting factories are situated concentrations of 0.1-0.5 µg/m^3 (weekly or monthly means) have been recorded. This may result in the inhalation of 2-10 µg cadmium per day. It should be remembered that a considerably larger percentage of inhaled cadmium compared with ingested cadmium will be expected to be absorbed.

Heavy smoking might also contribute. It can be expected that the smoking of 20 cigarettes per day will cause the inhalation of 2-4 µg of cadmium.

Table 3:1 DEPOSITION OF CADMIUM AROUND A CADMIUM-EMITTING FACTORY (mg/m^2/month). EMISSION OF CADMIUM: 460 KG/MONTH (from Olofsson 1970).

	Distance and direction from the source							
Period	0.1	0.3	0.3	0.5	0.7	1.0	10.4 km	Note
	S	NE	N	NNW	NE	SW	ENE	
5.7-7.8.68	(12.4)	(1.1)			(0.4)	(0.8)		Closed half the time
9.8-18.9.68	28	1.8			0.4	2.1		
26.9-25.10.68	18	0.7			4.0	3.5		
4.7-31.7.69	(1.3)			(1.4)	(1.3)	(1.3)		Closed
1.8-2.9.69	19			1.8	0.8	1.2		
5.9-9.10.69	8			3.0	2.0	1.1		
10.10-20.11.69	4			2.6	1.7	1.0		
29.4-8.6.70	8.8		1.2	0.5	0.6		0.2	
9.6-2.7.70	40		1.9	0.7	0.7		<0.03	
3.7-27.7.70	(4.6)		(0.9)	(0.1)	(<0.1)		(<0.1)	Closed
28.7-2.9.70	19		3.7	2.3	1.1		<2	
2.9-31.10.70	7.7		4.7	2.5	1.3		0.7	
2.10-2.11.70	14.8		5.3	2.4	0.8		0.3	

Table 3:2 DEPOSIT OF CADMIUM IN SOILS HELD IN TEST POTS
(Kitamura, personal communication)

Location	Time	Cd ppm
0.5 kilometers from emission source	0	0.7
	2 months	0.8
	1 year	6.2
	2 years	4.2
	3 years	9.4
Control area	0	0.7
	2 months	0.7
	1 year	0.7
	2 years	0.7
	3 years	0.6

Table 3:3 UPTAKE OF CADMIUM BY RICE PLANT AND WHEAT AS WELL AS YIELD. (Kobayashi, 1969).

Addition of Cd to soil (% CdO)	Rice			Wheat	
		Cd (ppm)			
	Yield (%)	Polished (10%)	Bran	Yield	Cd (ppm) whole grain
0	100	0.16	0.59	100	0.44
0.001	100	0.28	0.79	106	8.27
0.003	92	0.40	0.84	72	15.5
0.01	92	0.78	1.60	16	29.9
0.03	93	1.37	2.68	13	41.4
0.1	69	1.62	2.94	3	60.7
0.3	32	1.94	3.19	3	48.6
0.6	19	1.73	3.94	2	90.8
1.0	1	^{x}4.98		1	139.0

^{x}Unpolished

Table 3:4 CADMIUM IN FOOD (ppm wet weight).

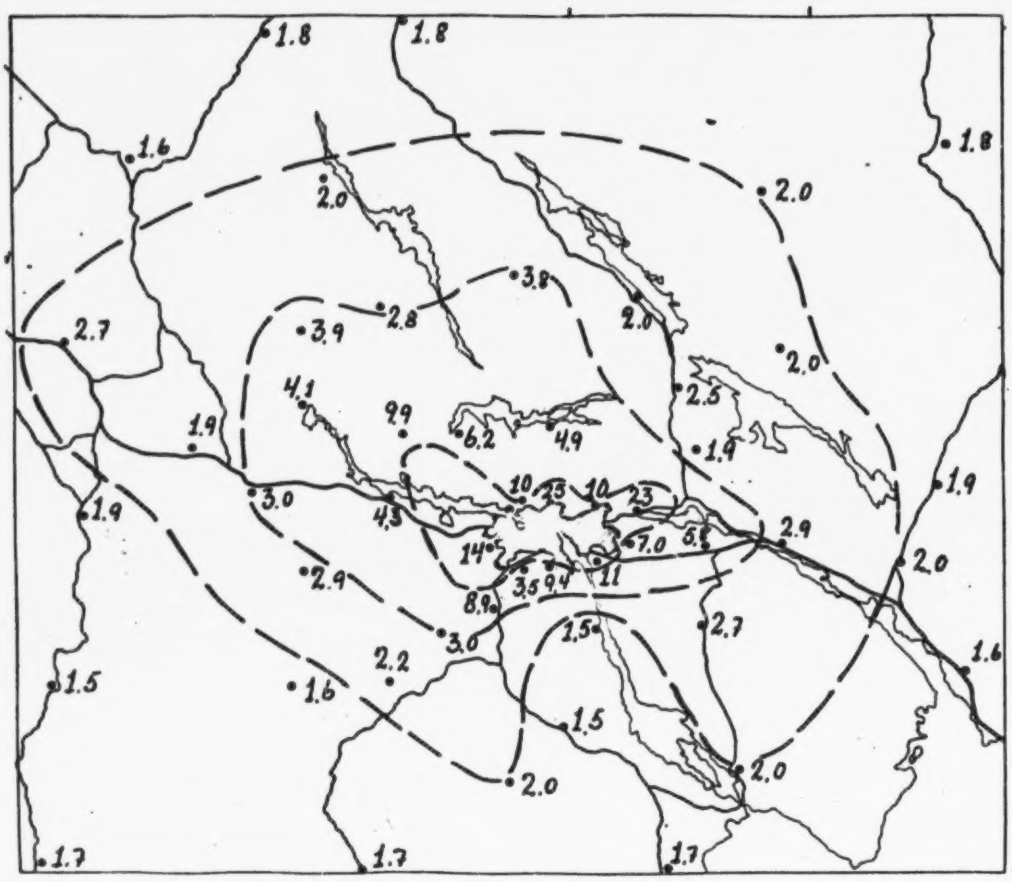
Country	Potato	Tomato	Wheat flour	Milk	References
U.S.A.	0.001	0	0.07	0.0015-0.004	Schroeder and Balassa (1961)
Western Germany	0.039	0.015	0.047	0.009	Essing et al. (1969)
Czechoslovakia	0.09	-	0.02	0.01	Lener and Bibr (1970)
Roumania	0.017	0.013	-	0	Rautu and Sporn (1970)
Japan (Non polluted areas)	0.038	0.032	0.025	0.003	Ishizaki, Fukushima and Sakamoto (1970)

Table 3:5 CONCENTRATIONS OF CADMIUM AND ZINC IN RENAL CORTEX FROM GUINEA-PIGS EXPOSED TO CIGARETTE SMOKE FOR 1 MONTH. MEANS AND STANDARD DEVIATIONS (Piscator and Rylander, unpublished data).

		ppm dry weight	
	n	cadmium	zinc
Controls	15	8.4±1.2	133±9
		$p < 0.025$	$p < 0.0025$
Smokers	22	10.8±2.8	151±19

Table 3:6 DAILY INTAKE OF CADMIUM VIA FOOD IN DIFFERENT COUNTRIES.

Country	Cd µg/day	Method	References
U.S.A.	4-60	Dithizone	Schroeder and Balassa 1961
Western Germany	48	Atomic absorption after extraction	Essing et al. 1969
Roumania	38-64	Dithizone	Rautu and Sporn
Czechoslovakia	60	Dithizone or isotope dilution or atomic absorption	Lener and Bibr
Japan (Non-polluted area)	59	Dithizone or atomic absorption after extraction	Yamagata and Shigematsu 1970


1.8
1.8
1.6
1.8
2.0
2.0
3.8
2.8
3.9
2.0
2.7
2.0
4.1
9.9
6.2
4.9
2.5
1.9
1.9
10
25
10
23
3.0
4.3
1.9
14
7.0
5.8
2.9
1.9
3.5
9.4
11
2.9
8.9
2.0
1.5
2.7
3.0
2.2
1.6
1.5
1.6
1.5
2.0
2.0
1.7
1.7
1.7

The isocurves are at the 10, 3 and 2 ppm levels.

Figure 3:1 Concentration of Cadmium in Moss (ppm dry weight) in an Area Surrounding a Cadmium-Emitting Factory (from Olofsson, 1970).

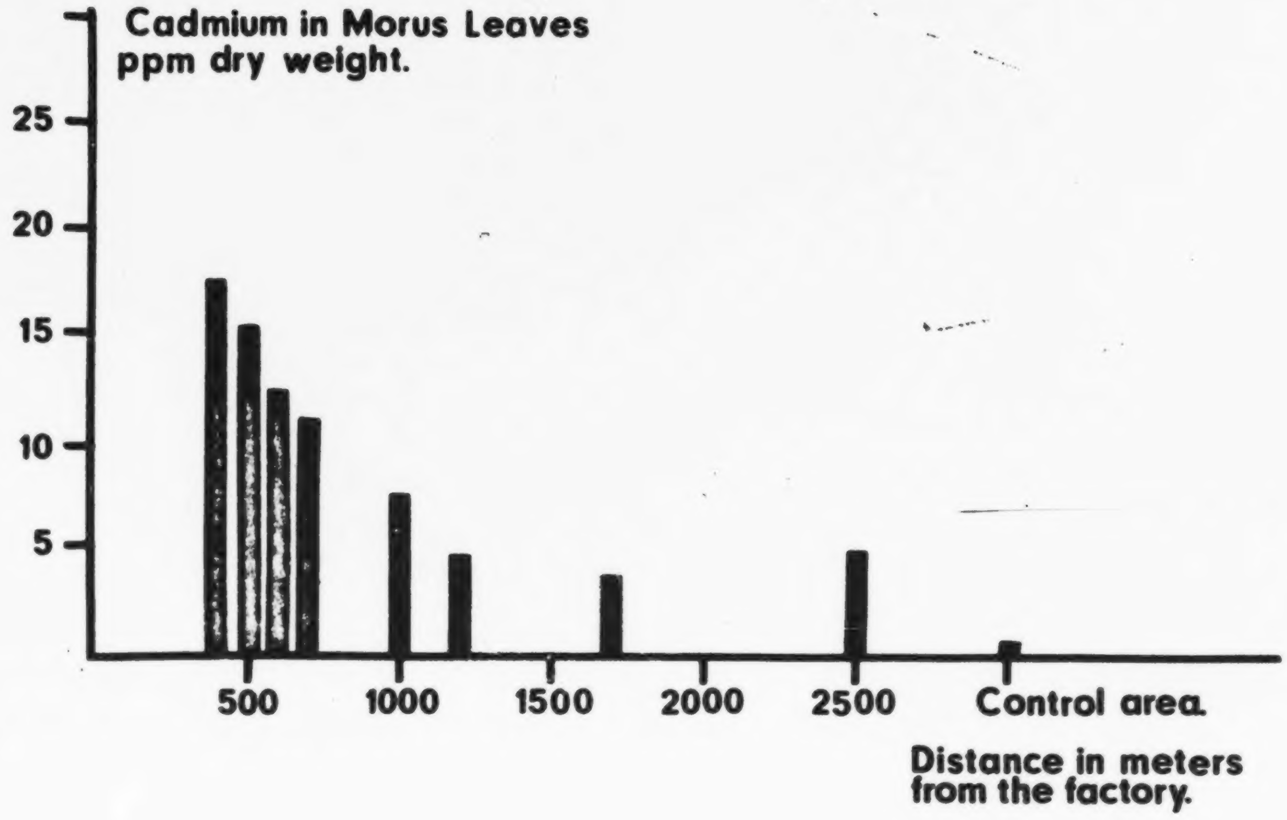


Figure 3:2 Concentration of Cadmium in Leaves of a Shrub in Relation to Distance from a Cadmium-Emitting Factory in Annaka City, Japan (from data by Kobayashi, 1969).

CHAPTER 4

METABOLISM

4.1 UPTAKE AND ABSORPTION

There is abundant evidence from human data that cadmium is found in different organs in concentrations increasing with age (see section 4.3.2). Data from workers exposed to cadmium as well as from animal experiments show also that cadmium is absorbed after exposure. For the human being there are two main ways of absorption, via the respiratory and gastrointestinal tracts.

4.1.1 Respiratory deposition, clearance and absorption

Some conclusions can be drawn from general knowledge about deposition and clearance of particulate matters in human beings. Apart from that, virtually all evidence of deposition, clearance and absorption of cadmium compounds is based on animal experiments.

4.1.1.1 Respiratory deposition

There are no data elucidating the immediate respiratory deposition after inhalation of cadmium or cadmium compounds. As cadmium exposure via inhalation will be in the form of an aerosol, there is every reason to believe that the deposition will follow general physical laws governing deposition of particulate matters (See e.g. Task Group on Lung Dynamics, 1966, Air Quality Criteria for Particulate Matter, 1969). Thus particle size will have a decisive importance and in humans breathing at a moderate work rate (20 l/min), the deposition in the pulmonary compartment will vary from about 10 to about 50 percent for particles with a mass median diameter of from about 5 microns to 0.01 microns.

4.1.1.2 Respiratory clearance

Although deposition patterns for particles of different sizes are fairly well known, clearance rates are not. However, certain general tendencies can be stated. Particles deposited on the bronchial mucosa, for example, are usually cleared by means of ciliar activity within hours. Thus, particles with high probability of deposition in the tracheobronchial compartment (relatively large particles) should be cleared relatively fast. For particles deposited in the pulmonary compartment, however, solubility and other physico-chemical properties of these particles will be the most important factors. Half-lives in the lungs are reported from a few days to about a year for different substances.. This question was dealt with to some extent by the Task Group on Lung Dynamics and is for the moment the subject of a new review by another task group under the ICRP on respiratory absorption and elimination mechanisms (chairman: Thomas Mercer, Ph.D., Rochester, N.Y.).

Concerning cadmium specifically, no precise information seems to be available on the several clearance mechanisms and their rate constants. However, some data have been reported by Harrison et al., 1947. They exposed dogs via an atomizer to a 25 percent solution of cadmium chloride over a period of 30 minutes. The exposure varied between 280-360 mg/m^3 with an LD_{90} of 320 mg/m^3 or 9600 $min \cdot mg/m^3$. They measured the concentration of cadmium in lungs, kidneys and liver at autopsies at different times after the exposure. The lung data are shown in figure 4:1.

As can be seen, clearance was rapid during the first two weeks with a half-life of approximately five days. With all probability, the initial clearance was still more rapid, even if this is not shown in the figures (no data from the very early post-exposure period are reported). The long-term clearance seems to have been slow as no further decrease was evident at the 10 weeks' observations. No information was given concerning particle size. The very high exposure, as a rule leading to the deaths of the animals, makes it impossible to extrapolate clearance rates for lower concentrations. An initial rapid clearance has also been reported by Gerard, 1944 (as quoted by Harrison et al., 1947). Gerard exposed mice to atomized radioactive cadmium chloride and found that about one-fourth of the cadmium initially retained in the lungs remained there for forty-eight hours.

A report by Barrett, Irwin and Semmons, 1947, should also be mentioned. They exposed groups of several animal species to cadmium oxide fumes in order to determine the toxicity of cadmium (see section 5.1). They reported retention values for cadmium in the lungs at different times after the exposure. The percentage retention (based upon cadmium concentrations in the lungs at post mortem and exposure data) varied between about 5 and 20 percent with an average of about 11 percent. No systematic differences were found between values from the early post exposure period and from the period beginning two weeks later. The exposure conditions varied considerably, however, and few conclusions can be stated concerning clearance rates.

4.1.1.3 Respiratory absorption

Abundant evidence verifies that cadmium can be found in different organs after industrial exposure in concentrations well above those found in the organs of "unexposed" subjects, (see 4.3.2). Thus, absorption via inhalation takes place. The information about exposure and lung deposition is, however, so scarce that quantitative evaluations of absorption rates from such data can not be made at this time.

Cadmium found in the internal organs such as the liver and kidneys could be the result of a direct absorption from the lungs or of secondary absorption via the gastrointestinal tract, following a mucociliary lung clearance. Which proportions of the absorption can be attributed to either of these two means, respectively, are not exactly known.

In the above mentioned report by Harrison, et al., 1947, the uptake in the kidneys and liver in dogs after an acute exposure was studied. The results are shown in figures 4:2 and 4:3. An increase in the concentration in the kidneys occurred simultaneously with a decrease in the lungs. Thus, the concentration in the kidneys reached about the same value (per gram dry weight) as had been present in the lungs during the first stages following exposure. Since no information was given concerning total lung and kidney weights or the initial lung deposition of cadmium, a precise quantitative analysis is not possible. The data do, however, fit with a high absorption, even taking into consideration that the initial lung deposition certainly was considerably higher than is evident from figure 4:1.

A conclusion that the absorption was high would also be reached if a calculation starts out from data concerning inhaled cadmium and recovered cadmium in liver and kidneys. The dogs were exposed to about 300 mg cadmium chloride/m^3 for 30 minutes and at least about 6 mg of cadmium/100 g dry weight (corresponding to about 2 mg/100 g wet weight) was found in the liver (figure 4:3) after a couple of days. The concentration in the kidneys was at least about 7 mg/100 g dry weight (figure 4:2), which would correspond to about 1.5 mg cadmium/100 mg wet weight. If it is assumed that about three fourths of the cadmium in the body (not counting the gut content) is in the liver and kidneys (see section 4.3.4) and that the weights of the dogs were 20 kg, with a lung ventilation of 300 l per hour (Altman and Dittmer, 1964) and a liver weight of about 4 percent and kidney weights of about 0.4 percent of the body weight, the following tentative estimations could be made. About 50 mg cadmium would have been inhaled and about 20 mg of cadmium would have been retained in the body a few days after exposure. This would mean a retention of about 40 percent of the inhaled cadmium.

In regard to the mode of absorption, it seems highly probable that a direct absorption was definitely the most important. The absorption was very rapid and studies of several animal species show that the absorption of cadmium via the gastrointestinal route is low (see 4.1.2.1).

Potts et al., 1950, reported about cadmium absorption and retention in mice a few hours after a single inhalation exposure to a radioactive cadmium chloride aerosol (particle size less than 2 μ). The concentration of cadmium in the exposure chamber was on an average 100 mg/m^3 and the exposure time, about 30 minutes. Because of several inconsistencies in the report, there are difficulties in interpreting the results as they are presented. It seems, however, that the data tend to show a retention of inhaled cadmium in internal organs (not counting the gut content) of about 10-20 percent.

Two chronic exposure studies, lasting for several months, both of which are discussed in detail in section 5.2.2, should be mentioned.

Friberg, 1950, in experiments with rabbits inhaling cadmium iron dust, found a high absorption as judged by concentrations of cadmium found in kidneys and liver. It can be calculated that the rabbits had inhaled, on an average, a total of about 190 mg of cadmium iron oxide dust, corresponding to about 120 mg of cadmium (data by Guyton, 1947, indicating a lung ventilation of about 50 l per hour for rabbits of about 2 kg, have been used in the calculations). The concentrations of cadmium in lungs, kidneys and liver at autopsy were reported as generally varying from about 5 to 15, 30 to 70, and 10 to 40 mg/100 g wet weight, respectively (spectrographic determinations). With weights of approximately 25, 15 and 65 g for lungs, kidneys and liver, respectively, the mean values for the organ amounts of cadmium can be estimated to have been as follows: the lungs contained about 2.5, the kidneys about 7.5 and the liver about 16 mg of cadmium, a total in these organs of about 25 mg retained cadmium. It can be expected that these organs contained about three fourths of the total body burden (see 4.3.4). It seems thus that the pulmonary absorption ($\frac{25 \cdot 10^4}{75 \cdot 120}$ percent) of the inhaled cadmium was high, about 30 percent. This of course means a considerably higher absorption of the cadmium that was deposited in the lungs.

Princi and Geever, 1950, made similar studies with dogs inhaling cadmium oxide dust and cadmium sulphide dust, respectively. Available data do not lend themselves to a detailed calculation like the one referred to above. The absorption must have been lower than in Friberg's studies, however, or the excretion of cadmium must have been very large, as the concentration of cadmium in the liver and particularly in the kidneys (dithizone method according to Church, 1947) was usually low. The kidney concentration varied from 2.1 to 13.3 mg/100 g - probably wet weight, but no information was given in the paper - in animals exposed to cadmium oxide, and from 0.02 to 4.3 in animals exposed to cadmium sulphide. Corresponding values in the liver were 1.2 to 4.7 and less than 0.04 to 1.0 mg/100 g. The reported kidney values are of the same magnitude as has been reported for human beings without occupational exposure (see section 4.3.2.1). The liver values for dogs exposed to cadmium oxide dust are considerably higher than those found in non-occupationally exposed human beings.

The difference in absorption found by Friberg as compared to that reported by Princi and Geever is not easily explained. Of some relevance could be that the U.S. cadmium dust differed from the Swedish dust in regard to solubility in water. The Swedish dust was more soluble (Ahlmark, Friberg and Hardy, 1956).

4.1.1.4 Conclusions

It is clear that cadmium can be absorbed and retained to a considerable degree in the body after inhalation. The absorption is primarily direct from the lungs.

Observations on human beings do not give quantitative data on absorption and retention. Animal experiments speak in favor of a retention of between 10-40 percent of inhaled cadmium. A considerable difference might well exist for different cadmium compounds.

There is a great need for more detailed studies on the absorption and retention of different cadmium compounds after inhalation. Studies should be carried out on different species and in connection with acute as well as chronic exposures.

4.1.2 Gastrointestinal absorption

4.1.2.1 In animals

4.1.2.1.1 Single exposure

Several reports have described the fate of a single oral dose of radioactive cadmium. Decker, Byerrum and Hoppert, 1957, gave about 6.6 mg/kg of ^{115}Cd as the nitrate to rats in stomach tube and after 8 and 24 hours found 98-99 percent in the stomach, the gut and the feces. These results would indicate an absorption rate of 1-2 percent. Cotzias, Borg and Selleck, 1961, gave 40 μCi ^{109}Cd as the chloride to mice by intubation and found that after 4 hours, 0.5-8 percent had been absorbed (mean not given). Richmond, Findlay and London, 1966, gave ^{109}Cd (dose and compound not stated) to mice by intubation. They found a mean retention after a few days of about one percent, (range: 0.5-3 percent) which means that on an average at least one percent had been absorbed. Miller, Blackmon and Martin, 1968, and Miller et al., 1969, gave goats ^{109}Cd-chloride (0.04-0.06 mg/Cd per goat) in gelatine capsules and found that more than 90 percent of the dose had been excreted in the feces after 14 days. The absorption rate was not calculated, but as Miller et al., 1969, estimated, total body retention was 0.3-0.4 percent of the given dose and urinary excretion was insignificant. Thus, not more than a few percent of the dose can have been absorbed.

Suzuki, Taguchi and Yokohashi, 1969, gave mice on a normal diet 0.08 mg of ^{109}Cd as the chloride by stomach needle. They followed the whole body retention (digestive tract with contents removed) between 0.5 and 164 hours in groups of three mice. Maximum retention was found after 11 hours, when 7 percent of the dose was in the body (range: 4.5-12 percent). After 164 hours, 1.6 percent (range: 1 - 2.3 percent) was present. Kitamura (personal communication) found that about 2 percent was retained after 24 hours when mice were given a single oral dose of 250 μg cadmium nitrate. Tomita and Togo (personal communication) obtained similar values (2.1 percent 24 hours after exposure and 1.8 percent 76 hours after exposure).

4.1.2.1.2 Repeated exposure

Decker et al., 1958, gave rats cadmium in drinking water in concentrations ranging from 0.1-10 ppm during 6 and 12-month periods. (This experiment will also be discussed in section 4.2.2.2). They did not measure total body retention, but did determine the percentage of the administered dose retained in kidney and liver after one year. As these organs will accumulate most of the cadmium, this estimate may indicate the whole body retention. Less than one percent of the total ingested amount had been retained in these organs (0.3-0.5 percent at all exposure levels). If it is assumed that 50-75 percent of the total body burden is in liver and kidney (see 4.3.4), total retention would be less than one percent. As urinary excretion and excretion into the intestines are almost insignificant before any toxic effects are seen (see section 4.2.4), this would mean that absorption would be of the same magnitude as the retention, or around one percent on the average.

Miller et al., 1967, administered about 5 mg Cd/kg to cows daily for two weeks. During the second week, cadmium excretion in feces was determined. Finding that 82 per cent of the daily dose was excreted, they concluded that 18 per cent was retained. Until more data have been obtained with regard to passage time of cadmium in the intestinal tract of cows, this figure must be regarded with caution, especially as the cow does not seem to accumulate cadmium to any large extent. Investigations on cows in cadmium contaminated areas in Sweden have shown renal levels of cadmium around 1-2 ppm, wet weight, indicating a low absorption rate (Piscator, unpublished data).

4.1.2.1.3 Influence of dietary factors upon absorption of cadmium

4.1.2.1.3.1 Calcium

It has been indicated in several reports concerned with the relationships among hardness of water, metal uptake and toxicity, that calcium may play an important role in the uptake of metals from the intestines. Schroeder, Nason and Balassa, 1967, gave rats 5 ppm cadmium in "hard" and "soft" drinking water during one to two years. Since the diet contained adequate amounts of calcium, however, the difference in total intake of calcium was only about 5 per cent. The authors found no difference between the groups in the accumulation of cadmium in liver and kidney and concluded that the hardness of the water was not in itself an important factor. Larsson and Piscator (to be published) gave female rats on low and high calcium diets 25 ppm Cd as the chloride in drinking water for one and two months. They found that the rats on the low calcium diet had accumulated about 50 percent more cadmium in liver and kidney than the rats on the high calcium diet, indicating a higher absorption in the former group, as there is no reason to believe that there would be differences in excretion (see table 4:1).

In addition to the results of these experiments, an influence of calcium on cadmium transport through the digestive tract has been found. Fleischman et al., 1968, and Suzuki, Taguchi and Yokohashi, 1969, found that a low content of calcium in the diet caused a slower passage of cadmium through the digestive tract compared with high calcium diets in rats and mice.

4.1.2.1.3.2 Vitamin D

Worker and Migicovsky, 1961, found that the uptake of cadmium in the tibia after an oral dose of ^{115}Cd was greater in rachitic chickens under treatment with Vitamin D than in untreated chickens. They concluded that this difference was due to the effect of Vitamin D on the intestinal absorption of cadmium, as there was no difference between similar groups in uptake in bone when ^{115}Cd was injected.

4.1.2.1.3.3 Protein

Fitzhugh and Meiller, 1941, mentioned briefly that the toxicity of cadmium was increased by a low protein diet. Suzuki, Taguchi and Yokohashi, 1969, gave mice low and high protein diets for 24 hours before and after an oral dose of ^{115}Cd-chloride. The low protein diet gave considerably higher levels of cadmium in kidney, liver and whole body, irrespective of calcium content in the diet, indicating an increase in the absorption of cadmium. Whole body retention was about 9 (range 5-14) and 4.5 (range 3-10) per cent in rats fed low and high protein diets, respectively.

4.1.2.2 In human beings

The absorption can theoretically be studied through long-term balance studies on intake and excretion of cadmium or on intake and body burdens of cadmium found at autopsies. Long-term balance studies have been performed on three subjects (Tipton, Stewart and Dickson, 1969, and Tipton and Stewart, 1970). Cadmium was determined daily by atomic absorption (without extraction) in the diet, in the urine and in the feces during 140-347 days. The mean daily intake of cadmium was about 170 μg and the mean daily fecal excretion was about 40 μg. This would indicate an absorption of about 75 percent. In Chapter 2 it is mentioned that sodium chloride is an interfering substance causing an increase in absorption when cadmium is determined by atomic absorption. It is highly probable that in the above mentioned investigations the amount of sodium chloride in the diet has interfered with the cadmium determinations. This is supported by the fact that much lower values for cadmium in food (see table 3:5) have been obtained when the metals have been extracted before analysis. The values for fecal excretion are within the range reported by other authors (see section 4.3.3.2). Schroeder and Balassa, 1961, by using the dithizone method, estimated that the daily intake of cadmium in the United States could vary between 4 and 60 µg, depending upon foods chosen. Boström and Wester, 1968, found that in one healthy subject, studied for two periods of five days, the intake of cadmium was 12 µg per day in both periods and the mean fecal excretion of cadmium was 5.3 and 4.5 µg, respectively. The determinations were done with neutron activation. These data do not lend themselves to an evaluation of absorption, due to the short observation period.

The body burden of cadmium for a "standard man", 50 years of age, in the United Kingdom and Sweden can be estimated to be about 15-20 mg and in the United States to about 30 mg (see section 4.3.4). The cadmium content in food during the past 50 years can of course not be estimated with any high degree of certainty. If no substantial changes have taken place over the years, it would probably be somewhere between 20 and 50 µg with the higher values probably in the United States.

The newborn contains a total of about only one µg of cadmium. Thirty mg at the age of 50 would mean a daily absorption of at least 1.6 µg. In this calculation, a linear absorption rate over the years has been assumed and also that the excretion of cadmium is negligible. In any case the last assumption is with all probability valid (see section 4.2.4).

An absorption of 1.6 µg/day could be reached with an absorption rate of 3-8 percent, depending on variations in the daily intake between 20-50 µg. Absorption via ambient air or industrial exposure has been neglected. Furthermore, these calculations are based on averages. Individual variations have not been taken into account.

4.1.2.3 Conclusions

The results from experiments on animals, mainly rats and mice, indicate that less than 10 percent of an oral dose is absorbed. Most reports show an absorption rate of about 2 percent. At present there are no experimental data that help us in making an estimate with regard to absorption in human beings. One way to estimate the absorption would be to use animal data. This would mean that the most probable average absorption rate would be about 2 percent, but with a large individual variation. Further, absorption of cadmium has been shown to be influenced by other factors in the diet, such as the amount of calcium, Vitamin D and protein. The cadmium absorption is increased considerably by a low calcium or a low protein intake. There is no reason to believe that the same should not hold true for human beings.

Estimations based on body burdens of cadmium found at autopsies of the "standard man" in the United States together with estimated intake over a 50 year period point to an average absorption of somewhere between 3-8 percent, e.g. not very much different from the estimations based on animal data.

Until more exact data are obtained, an absorption rate of about 10 percent of ingested cadmium must be considered quite possible in the individual case under certain circumstances, such as calcium and protein deficiency.

It is extremely important to study the question in human beings further, as an absorption of 2 percent, 5 percent or 10 percent would make a substantial difference from a toxicological point of view as will be discussed later.

4.1.3 Placental transfer

4.1.3.1 In animals

Berlin and Ullberg, 1963, gave pregnant mice single intravenous ^{109}Cd-chloride injections of 10 µCi, carrier free ^{109}Cd on the 18th day after conception. They could not detect any cadmium in the fetus but could note an accumulation of cadmium in the placenta. After giving a single intravenous dose of 0.5-0.85 mg Cd/kg to pregnant hamsters on the 8th day of gestation, Ferm, Hanlon and Urban, 1969, found relatively high concentrations of cadmium both in the placenta and in the fetus. The dose was considerably larger than the one given by Berlin and Ullberg. In addition, Ferm, Hanlon and Urban administered the metal at that period during which the major organ systems are being established in the hamster embryo and the embryologic activity is high, whereas Berlin and Ullberg injected the cadmium during the last few days of pregnancy.

By exposing rats from the day of conception to cadmium oxide dust in concentrations of about 3 mg/m^3, Cvetkova, 1970, found that the livers of the embryos after 22 days contained more than twice the amount of cadmium contained in controls.

Large doses of cadmium will destroy the placenta, especially the fetal part, as shown by Parízek, 1964, who gave rats subcutaneous injections of 4.5 mg Cd/kg on the 17th-21st days of gestation. Parízek, 1965, showed that 2.5 mg/kg by the subcutaneous route had the same effect. He also noted that the pregnant rat was more susceptible to the action of cadmium than the non-pregnant rat. Parízek et al., 1968, found that the simultaneous administration of sodium selenite protected the fetus from the destructive action of cadmium, but increased the uptake of cadmium in the placenta. Holmberg and Ferm, 1969, found that selenite protected the hamster embryo after intravenous injection of 2 mg Cd/kg. Of additional interest is the fact that chelating agents, such as EDTA, increase the transplacental passage of cadmium (Eybl, Sýkora and Mertl, 1966^{b}).

4.1.3.2 In human beings

Henke, Sachs and Bohn, 1970, analysed liver and kidney samples from newborns in West Germany by neutron activation and found between 4 and 20 ng/g wet weight in four kidneys. The concentration was less than 2 ng/g in the liver. This means that the total content of cadmium in the newborn will be less than 1 µg.

Cadmium will accumulate in the placenta during pregnancy. Concentrations of less than 10 ng/g wet weight have been found in Swedish women (Piscator, unpublished data). As the placental weight is about 500 grams, this means that not more than 5 µg will accumulate. In comparison, a human kidney will usually accumulate about 100 µg during a 9-month period (see section 4.3.2.1).

4.1.3.3 Conclusions

Animal experiments indicate that the placenta constitutes a barrier against transfer of cadmium when small doses are given. However, when large doses are given, cadmium may destroy the placental barrier and enter the fetus. In human newborns, the total body content of cadmium is small, less than 1 µg.

4.2 TRANSPORT, DISTRIBUTION AND EXCRETION OF CADMIUM IN ANIMALS

Cadmium will be found in blood, internal organs and excreta after absorption following exposure via air, oral intake or injection. In the following sections, the metabolism after both single and repeated exposure will be considered. The distribution of cadmium after respiratory exposure has been discussed in section 4.1.1.3 and will not be further treated in this section.

4.2.1 Uptake to and clearance from blood

In section 4.1.2 it was mentioned that after oral exposure only a few percent of the dose was absorbed. Attempts to determine levels of radioactive cadmium in blood after a single dose have not been successful, so only cadmium in blood after injection will be considered in this section.

4.2.1.1 Fate of cadmium in blood after single injection

4.2.1.1.1 First hours after injection

Intravenous route

During the first hours after injection, cadmium is found mainly in the plasma, as seen in dogs (Walsh and Burch, 1959), in rabbits (Kench, Wells and Smith, 1962) and in rats (Perry et al., 1970). The last mentioned authors found 98-99 per cent of the blood cadmium in the plasma 0.5 and 8.5 minutes after injection and Kench, Wells and Smith found 90 and 80 per cent 9 minutes and 1 hour, respectively, after injection. Perry et al. found that about two thirds of the plasma cadmium was dialyzable during the first 8.5 minutes.

The clearance of cadmium from the plasma is characterized by an initial rapid phase followed by a slower phase, as shown in figure 4:4 from Walsh and Burch, who gave dogs 0.24-0.36 mg ^{115}Cd/kg as cadmium nitrate. Perry et al. also found a rapid clearance in rats during the first 8.5 minutes after an injection of 0.2

mg ^{115}Cd/kg. Kench, Wells and Smith gave a large dose, about 4 mg ^{115}Cd/kg as the sulphate to two rabbits and found that after 9 minutes about 45 per cent of the dose remained in the plasma and after 1 hour, 6.5 per cent. As they gave a lethal dose and one rabbit died within 6 hours, their data can not be regarded as representative for the rabbit.

Perry et al. found a small uptake of about 2 per cent of the blood cadmium in the erythrocytes after 0.5 minutes. Though Walsh and Burch mentioned that a small but constant amount of cadmium was found in the cells, they did not report the values.

Intraperitoneal route

After an intraperitoneal injection of soluble cadmium compounds, the maximum blood levels are reached within very short periods. In studies by Johnson and Miller, 1970, who gave rats ^{109}Cd (0.01-0.02 mg/kg) as the chloride, the maximum concentration was reached after 5 minutes. In similar studies (Perry and Erlanger to be published) maximum blood levels were found 8 minutes after injection (rats, ^{115}Cd as chloride, 0.06-0.96 mg Cd/kg). In the last mentioned experiment, it was calculated that 3 per cent of the injected dose was circulating in the blood. In the study by Johnson and Miller, the blood level 80 minutes after the injection was only 12 per cent of the maximum value, indicating a rapid initial clearance from the blood. Perry and Erlanger reported that the concentrations 120 minutes after the injections had decreased to 44 and 16 per cent of the maximum concentrations after injections of 0.24 and 0.96 mg Cd/kg, respectively. They further stated that only a few per cent of the cadmium in the blood were in the red cells and that part of the plasma cadmium was dialyzable.

Subcutaneous route

After a subcutaneous injection of soluble cadmium compounds, cadmium will soon appear in the blood and maximum levels have been reported after 10 minutes by Johnson and Miller, 1970, and after 60 minutes, Eybl, Sýkora and Mertl, 1966a. Johnson and Miller gave rats 0.01-0.02 mg ^{109}Cd/kg as the chloride. They found that there was a rapid initial clearance, so that 80 minutes after injection, the concentration in whole blood was only 16 per cent of the 10 minute value. Eybl, Sykora and Mertl gave rats 1.25 mg ^{115}Cd/kg as the chloride, and found that the concentration in blood after 1 hour was higher than after 20 minutes. The difference in the results will probably be explained by the considerably larger dose given by the latter authors, which will have resulted in a large deposit at the injection site.

During the first 12 hours, there will be a decrease in blood levels, as shown in Fig. 4:5, where data from the experiment by Eybl, Sykora and Mertl, 1966a,are shown together with data from Gunn, Gould and Anderson, 1968 a, who gave mice 1.4 mg ^{109}Cd/kg as the chloride, and from Lucis,Lynk and Lucis, 1969, who gave rats a tracer dose of ^{109}Cd as the chloride. This decrease is mainly due to a decrease in plasma levels of cadmium, as shown in Fig. 4:6, where data are taken from the experiments by Eybl, Sykora and Mertl, 1966a,and Lucis, Lynk and Lucis, 1969. In Figure 4:6, it will also be seen that there is an initial uptake in the cells, and that the clearance from the cells during the first 12 hours is smaller than the clearance from the plasma, so that after about 12 hours, concentrations are of the same magnitude in cells and plasma.

4.2.1.1.2 First weeks after injection

Whereas there are large differences in distribution during the first hours after injection, depending on how fast cadmium enters the blood, distribution and clearance mechanisms seem to be more similar when some time has elapsed since injection. Figure 4:5 shows the levels in blood in animals exposed by the subcutaneous route. Blood levels decrease during the first 12 hours. Then a change occurs: the blood levels increase again. In rats, this increase is due to an increase of the cadmium content of the erythrocytes, as shown in figure 4:6.

It should be noted that in both the experiment by Gunn, Gould and Anderson, 1968a, on mice and by Lucis, Lynk and Lucis, 1969, on rats, there was a decrease after the 7th day. Niemeier, 1967, followed rats after an intravenous injection of ^{115}Cd sulphate and found that after 16 days the cadmium level in blood was more than twice the level at day one. In the goat (Miller, Blackmon and Martin, 1968) and the hamster (Ferm, Hanlon and Urban, 1969), a rise in the cadmium level between day 1 and day 7 and day 1 and day 2, respectively, after intravenous injections, has been noted.

These results indicate that after the first rapid clearance of cadmium from blood, a second phase will occur in which cadmium will be released into the blood, probably from the liver, where the main part of the injected cadmium will be found (see section 4.2.2).

4.2.1.2 Fate of cadmium in blood after repeated injections

Friberg, 1952, found, in rabbits given subcutaneous injections of ^{115}Cd-sulphate (0.65 mg Cd/kg six days a week for 4 and 10 weeks), that the cadmium levels in blood were 45 and 100 µg/100 ml blood, respectively. He could not demonstrate the presence of cadmium in the plasma and concluded that the cadmium was in the blood cells. Truhaut and Boudene, 1954, gave two rabbits subcutaneous injections of cadmium sulphate, 13 injections of 2.1 mg/kg and 19 injections of 1.8 mg/kg. They found that the concentration in the erythrocytes was 18 and 10 times greater, respectively, than in the plasma. Friberg, 1955, made new experiments with similar exposure conditions as in 1952. In one experiment rabbits were given ^{115}Cd during 70 days. In another, they were first given the isotope for 50 days and then ordinary cadmium for the remaining 20 days. In both experiments cadmium levels rose steadily until the 50th day, at which time they were around 200 µg/100 ml..In rabbits given further injections of ^{115}Cd, blood levels of the isotope remained around 200 µg/100 ml after 10 weeks. In rabbits given nonradioactive cadmium, a decrease in ^{115}Cd levels to about 125 µg/100 ml in 20 days was found. The results show that at a certain cadmium level in the blood a plateau is reached. A continuous exchange between cadmium accumulated in the blood and newly administered cadmium takes place.

Carlson and Friberg, 1957, gave 1 mg ^{115}Cd/kg to two rabbits daily for one week. The animals were killed 2 days after cessation of exposure. They also gave 0.65 mg ^{115}Cd/kg to two other rabbits daily for three weeks. The animals were killed 3 weeks after cessation of exposure. One to six percent of the cadmium in whole blood was found in the plasma. When red cells from these rabbits were hemolyzed and centrifuged, all cadmium was recovered in the supernatant. Forty and thirty-seven per cent, respectively, of the cadmium in the hemolysate was found to be dialyzable through polyvinyl tubings. Separation by zone electrophoresis in starch of hemolysates from two other rabbits exposed 2 and 4 weeks showed that most of the cadmium in the hemolysate was in the same fractions as hemoglobin and the authors concluded that part of the cadmium was bound to hemoglobin.

4.2.2 Tissue distribution and retention

4.2.2.1 Single exposure

Oral route

The amount absorbed after a single dose is small, as has been discussed in section 4.1.2. The distribution in organs has been studied by several authors. Decker, Byerrum and Hoppert, 1957, gave rats ^{115}Cd-nitrate (6.6 mg Cd/kg) and determined cadmium distribution from 8 to 360 hours after the dose. After 8 hours the largest total amount of cadmium was in the liver while the highest concentration was in the kidneys. After maximum concentrations in both organs were reached at 72 hours after exposure, a slow decrease seemed to occur in both organs. Miller, Blackmon and Martin, 1968, gave a single oral dose of ^{115}Cd-chloride to goats (0.04 mg Cd/goat) and found that after 14 days the concentration in the kidneys was nearly twice as high as that in the liver. Miller et al., 1968, gave about 0.06 mg of ^{109}Cd to groups of goats, one group of which had been pretreated one week with a diet containing 100 ppm of nonradioactive cadmium. Determination of ^{109}Cd content in organs was made 14 days after exposure. They did not find any differences between the groups.

Suzuki, Taguchi and Yokohashi, 1969, put mice on diets with high calcium-low phosphorus and low calcium-high phosphorus content, respectively, for 10 days and then gave them a single dose of ^{109}Cd-chloride (about 0.08 mg Cd/mouse). Liver and kidney levels were measured after 24 and 72 hours, respectively. No difference was found between the groups. However, within the groups differences in levels at the two times of measurement could be seen. After 72 hours both kidney and liver levels were only half of the 24 hour values, indicating rapid clearance.

Injection route

The distribution of cadmium will vary considerably depending on the dose and the time. The experiments mentioned in 4.2.1.1, in which the fate of cadmium in blood after a single dose was followed showed in addition that most of the cadmium initially goes to the liver and relatively small amounts to the kidneys. With increasing time after exposure, the kidney levels will increase and will become higher than liver levels.

Gunn and Gould, 1957, gave a single intracardiac injection of ^{115}Cd-nitrate to rats (dose not stated) and followed the animals for up to 8 months. From their data it is seen that during the first month there was a decrease in liver levels of ^{115}Cd and an increase in kidney cortex levels, so that after a month of exposure, the concentration in the cortex was the same as that in the liver (Figure 4:7). During the following months liver levels decreased very slowly while levels in cortex increased so that after 5 months the ratio between cortex and liver levels was 2.4 and after 8 months, 4-5. The levels in kidney medulla also increased with time and after 8 months they exceeded liver levels. In addition, the authors observed that age could influence uptake in the kidney in rats from 1-7 weeks old, so that the younger the rat, the less the uptake. To the contrary, liver levels did not vary with age. This was explained as due to the smaller number of nephrons in the younger rats. Decker, Byerrum and Hoppert, 1957, injected ^{115}Cd-nitrate into rats by the intravenous route (approximately 0.65 mg Cd/kg). They found that from 4 hours to 5 weeks after injection the liver contained between 62 and 70 per cent of the injected dose. The kidney contained between 1.6 and 2.4 per cent of the dose from 4 hours to 2 weeks. Then, at five weeks, 5.1 per cent of the total dose was found in the kidney.

Burch and Walsh, 1959, found that in dogs given an intravenous injection of ^{115}Cd-nitrate (0.24-0.36 mg Cd/kg), the concentration in the liver during the first 24 hours was considerably greater than that in the kidneys. After 20-30 days, the concentration in the kidneys was 50-100 per cent of the liver levels. Lucis, Lynk and Lucis, 1969, followed cadmium concentrations for 14 days after giving a tracer dose of ^{109}Cd-chloride to rats by subcutaneous injection. They found that already 2 hours after injection kidney levels were slightly higher than liver levels and that 10 hours after injection, the concentration in the kidneys was about 50 per cent higher than that in the liver. At 2 weeks both the kidney and liver concentrations had increased compared with the concentrations at 30 hours. Miller, Blackman and Martin, 1968, investigated the distribution in goats 14 days after a single intravenous administration, using ^{109}Cd (0.04 mg/goat). Concentrations in liver were three times higher than those in kidney, whereas after an oral dose of the same size, the concentrations in kidney were nearly twice as high as those in liver. Lucis and Lucis, 1969, studied four strains of mice and found considerable differences in organ concentrations 24 hours after subcutaneous injection. Liver levels varied between 37 and 52 per cent of injected dose per gram.

The liver and the kidney seem to be the two organs of greatest interest with regard to cadmium storage. Cadmium will, however, be found in most compartments of the body. The pancreas and the spleen will store relatively large amounts. Nordberg and Nishiyama (to be published) found that in mice cadmium levels in the pancreas increased with time and exceeded liver levels 110 days after injection (5 µg Cd/kg,intravenous). Figure 4:8 shows the distribution of ^{109}Cd 110 days after a single injection. Berlin and Ullberg, 1963, did not find cadmium in osseous tissue after a single intravenous injection of ^{109}Cd-chloride, but they did observe that cadmium was accumulated and retained in bone marrow and periostium. They detected traces of cadmium in the brain. Their finding of an accumulation in the testis and the hypophysis is also of interest.

4.2.2.2 Repeated exposure

Oral route

Long-term experiments with exposure via the oral route have been made by Decker et al., 1958, who gave cadmium in drinking water to rats for 6 and 12 months. The concentrations of cadmium in the water were 0, 0.1, 0.5, 2.5, 5 and 10 μg/ml. They found that the concentrations in kidneys and liver were roughly proportional to the intake of cadmium. It was also found that the larger the dose, the larger the ratio became between concentrations in liver and kidneys, as shown in table 4:2. Data from a similar experiment on dogs by Anwar et al., 1961, are included in the table.

Injection route

Friberg, 1952, gave subcutaneous injections of ^{115}Cd-sulphate (0.65 mg Cd/kg) to rabbits 6 days a week for 4 and 10 weeks, respectively. Four rabbits exposed for 4 weeks had mean levels of 1160, 600, 75 and 45 ppm Cd (dry weight) in liver, kidney, pancreas and spleen, respectively. After 10 weeks the corresponding figures were 1480, 1000, 193 and 180 ppm. During the period of 4-10 weeks of exposure the accumulation rate of liver and kidney decreased, that of spleen increased and that of the pancreas showed no change. Since cadmium will be excreted during this period (see section 4.2.4), these results are partly explained. Friberg, 1955, made a new experiment with similar exposure for 10 weeks, but he gave one group nonradioactive cadmium for the last 20 days. After 10 weeks liver levels of ^{115}Cd were considerably higher than kidney levels. In animals to which nonradioactive cadmium had been given for the last 20 days of the exposure time, the level of radioactive cadmium in the kidneys was only about half of the level in animals given the isotope during the entire period. This indicates that during those 20 days the kidneys had excreted part of the stored cadmium.

Axelsson and Piscator, 1966a, gave rabbits cadmium chloride (0.25 mg Cd/kg) by subcutaneous injections 5 days a week for 11-29 weeks. There was an increase in liver and renal cortex levels up to 17 weeks. The levels at that time were about 450 and 400 ppm wet weight, respectively. Further exposure did not increase the concentration in the liver. In the renal cortex, there was a decrease so that the concentration was about 275 ppm wet weight after 23 and 29 weeks. As excretion of cadmium was low until after 17 weeks but then increased considerably (see section 4.2.4.1), these findings agree with Friberg's results showing first an accumulation stage, followed by an excretion stage. Piscator and Axelsson, 1970, found in a follow-up of a group exposed for 24 weeks under similar conditions (0.25 mg Cd/kg, subcutaneous injection, 5 days a week) and killed 7 months after the last injection that kidney levels had only decreased a little compared with the above mentioned concentrations at 23 or 29 weeks of exposure. Liver levels were about half of the levels at the time exposure ceased.

Bonnell, Ross and King, 1960, gave intraperitoneal injections of cadmium nitrate to rats (0.75 mg Cd/kg 3 days/week for 5-6 months). Exposure was then discontinued for two months, after which injections were resumed for some animals (0.25 mg/kg). Other animals received no further exposure. The total time for the experiment was 12 months. A linear increase of cadmium in liver was seen during the first three months, when a plateau was reached at about 350 ppm wet weight (see figure 4:9). It is conceivable that at this time excretion of cadmium began. Urinary cadmium was, however, not determined. The resumed exposure did not increase the levels. A gradual decrease was actually seen. In the kidneys linear increase was also seen during the first three months, when a plateau was reached at about 275 ppm wet weight (figure 4:10). At the end of the experiment the levels were lower than at three months. No difference in cadmium levels between animals who received further injections during the last five months and those animals who did not, could be detected.

4.2.3 Distribution within organs

4.2.3.1 Single exposure

Friberg and Odeblad, 1957, gave a single subcutaneous injection of ^{115}Cd-sulphate (1.3 mg Cd/kg) to rats and killed the animals after 5.5 and 24 hours respectively. The renal cortex accumulated more cadmium than the medulla. In the pancreas distribution was equal between exocrine and endocrine parts. Gunn and Gould, 1957, gave a single intracardiac injection of ^{115}Cd to rats and found a selective accumulation of cadmium in the renal cortex. They followed the animals for 150 days. At that time the cortex contained 4 times more cadmium than the medulla.

Berlin and Ullberg, 1963, gave a single intravenous tracer dose of ^{109}Cd-chloride to mice and studied the distribution by autoradiography. The animals were killed at times after injection varying from 5 minutes to 16 days. In the renal cortex the authors found scattered areas with high activity. In the liver the distribution was uniform during the first 24 hours, but after 8 days a higher concentration was found in the periphery of the liver lobules. In the testes especially the interstitial tissue contained cadmium.

A special study on the distribution in the kidneys was made by Berlin, Hammarström and Maunsbach, 1964. Mice were killed 24 hours after a single intravenous tracer dose of ^{109}Cd-chloride. In the renal cortex the largest accumulation was found in the outer cortex and corresponded to proximal tubules. Especially the first segment of the proximal tubules showed high activity. The glomeruli did not retain cadmium to the same degree.

The subcellular distribution in the liver has been studied by Kapoor, Agarwala and Kar, 1961. Rats were given a single subcutaneous injection of cadmium chloride (10 mg/kg) and the livers were fractionated by ultracentrifugation from 6-168 hours thereafter. The total concentration of cadmium was the same at the different times. However, there was a change in distribution with time, so that at 6 and 12 hours after injection about 30 per cent was in the supernatant, whereas at 24, 48 and 168 hours, about 60 per cent was in that fraction. This corresponded to a decrease in the nuclear, mitochondrial and microsomal fractions.

Twenty-four hours after a single subcutaneous injection of ^{109}Cd-chloride to mice and to rats, cadmium was distributed so that 80 per cent was in the supernatant (Shaikh and Lucis, 1969, 1970). Nordberg, Piscator and Lind (to be published) found that change in distribution took place with time after a single injection of cadmium chloride (3 mg Cd/kg) in mice. During the first 24 hours almost more than 80 percent of the cadmium in the supernatant was in the high molecular weight proteins, as shown by gel filtration, whereas later a change occurred so that more than 50 percent of the cadmium was in a low molecular weight fraction, probably metallothionein. Shaikh and Lucis, 1970, had found a similar low molecular weight fraction in their experiment.

4.2.3.2 Repeated exposure

Friberg, 1952, gave rabbits subcutaneous injections of ^{115}Cd-sulphate 6 days a week for 10 weeks (0.65 mg Cd/kg) and found by autoradiography that in the kidneys the cortex contained 5 times more cadmium than the medulla. In the liver more activity was in the periphery of the lobules than in the inner halves. In the pancreas the glandular part accumulated cadmium, while no cadmium was found in the connective tissue. Friberg did not note any difference between the exocrine and the endocrine parts.

Long-term experiments on the rabbit by Axelsson and Piscator, 1966a, revealed that during exposure to subcutaneous injection of 0.25 mg cadmium/kg 5 days a week for 11-29 weeks, the ratio between cortex and medulla was 5.1 (2.5-9). In rabbits exposed in a similar way for 24 weeks and then followed for another 30 weeks, the ratio was 3.6 (2.4-5.5) (Piscator and Axelsson, 1970).

By using a staining method for metals, Axelsson, Dahlgren and Piscator, 1968, found the main metal accumumlation in renal proximal tubules in the above mentioned rabbits. Considerably smaller amounts of deposited metals were found in the glomeruli, collecting tubules and medulla.

4.2.4 Excretion

4.2.4.1 Urinary excretion

When a single dose of cadmium has been given via the oral route or via injection, only a small amount has been detected in the urine. After a single oral dose of ^{109}Cd to goats, Miller, Blackmon and Martin, 1968, found that on days 1, 2, and 3-7, after exposure, 0.5, 1, and 0.1 per cent respectively of the absorbed amount were excreted via the urine. The original values have been recalculated to fit an assumed absorption of 2 percent. A dose of the same amount of cadmium as the oral dose in the previously mentioned experiment was administered by intravenous injection. Excretion values were 0.025, 0.004 and 0.002 percent. The authors pointed out that these values could be too high, as fecal contamination could increase the cadmium levels. In rats, Lucis, Lynk and Lucis, 1969, found that 1 per cent of a single subcutaneous injection of ^{109}Cd solution had been excreted with the urine after 1 week. Burch and Walsh, 1959, calculated the half-life after a single intravenous injection of ^{115}Cd as nitrate (5 dogs, followed for 20-30 days). It can be calculated from their data that it would take 3-7 years to eliminate 50 percent of the cadmium via the urine alone.

Friberg, 1952, gave subcutaneous injections of cadmium sulphate containing ^{115}Cd in daily doses of 0.65 mg Cd/kg to rabbits. When the excretion of the isotope was followed for 10 weeks, as shown in figure 4:11, it was found that for a period varying between 6 and 7 weeks, the daily cadmium excretion was very small, about 1 percent of the daily injected dose. During the last weeks of the experiment there was a sharp rise in cadmium excretion, up to about 100 times the amount excreted during the first weeks. This rise in cadmium excretion coincided with the appearance of proteinuria in the rabbits.

Further investigations were made by Friberg, 1955, under similar experimental conditions as above. One group of rabbits was given first radioactive cadmium for 50 days and nonradioactive cadmium for the remaining 20-50 days. Another group was given radioactive cadmium for 70 days, whereafter cadmium excretion was followed for another 30 days. During the administration of nonradioactive cadmium, the excretion of radioactive cadmium increased markedly. In the group that received no more cadmium whatsoever after the end of the exposure to radioactive cadmium, the concentration of radioactive cadmium in urine decreased rapidly. It was thus clearly demonstrated that, at the time kidney damage existed, the urinary cadmium excreted during exposure came partly from accumulated deposits.

Axelsson and Piscator, 1966a, gave rabbits 0.25 mg Cd/kg as cadmium chloride for 5 days a week for 6 months by subcutaneous injection. During the first 4 months there was an insignificant excretion of cadmium but in the last 2 months there was such a sudden rise in cadmium excretion that in some animals, the daily excretion exceeded the daily dose. The increase in urinary excretion of cadmium paralleled an increase in urinary protein. Six months after an exposure for 6 months two rabbits in a group of six still excreted large amounts of cadmium (Piscator and Axelsson, 1970).

In summary, there is evidence that during long-term exposure the excretion of cadmium with the urine is only about 1 percent of the dose. When renal dysfunction has occurred, there will be a sharp increase in excretion, however. In experiments on rabbits this increase was 50-100 fold.

4.2.4.2 Excretion via the alimentary tract

Animal experiments have shown that injected cadmium will be partially excreted with the feces. Decker, Byerrum and Hoppert, 1957, gave the rat a single intravenous dose of ^{115}Cd (0.63 mg/kg). After the first 24 hours, 7.3 per cent was found in the feces. After 77 hours 18.5 percent of the given dose had been excreted via feces.

Burch and Walsh, 1959, injected a single dose of ^{115}Cd (0.32-0.40 mg/kg) intravenously into dogs. They determined the amount of the isotope in feces from five dogs for 20-30 days. They calculated that 419-659 days were required for elimination of half of the injected cadmium by fecal excretion alone. Relatively large amounts of the isotope were in the gastrointestinal tract, especially the small intestine, the first two days after injection. Berlin and Ullberg, 1963, using whole-body autoradiography after a tracer dose of ^{109}Cd intravenously injected into mice, found that cadmium rapidly accumulated in the mucous membrane of the intestinal tract and that after 24 hours the cadmium in the mucosa seemed to decrease. Cadmium accumulated mainly in the secretory part of the gastric mucosa and in the colonic mucosa. The investigators could also find radioactivity in the contents of the stomach and colon 20 minutes after injection. When Lucis, Lynk and Lucis, 1969, gave a tracer dose of ^{109}Cd by a single subcutaneous injection into rats, they found that cadmium accumulated rapidly in the wall of the stomach and detected only traces in the contents of the stomach. In the intestines the wall of the small intestine had the largest concentration. Radioactivity in the intestinal contents increased during the first 24 hours.

Johnson and Miller, 1970, compared the results of single subcutaneous and intraperitoneal injections of ^{109}Cd (0.02 mg/kg) as chloride given to rats and with both techniques found cadmium in the duodenum after 2 1/2 minutes. Miller, Blackmon and Martin, 1968, gave a single intravenous dose of ^{109}Cd as chloride to goats and found that 5.6 percent was excreted via feces within 5 days.

Ceresa, 1945, determined the daily excretion of cadmium in 5 rabbits. The animals received 11 mg Cd/kg daily as the sulphate by the subcutaneous route, which resulted in the deaths of the animals after 7-9 days. During the period of exposure, the mean fecal excretion rate was 1.8 percent of the injected amount and slightly higher than the urinary excretion.

Long-term experiments have been performed by Axelsson and Piscator, 1966a, on rabbits given 0.25 mg Cd/kg as chloride 5 days a week for 29 weeks by subcutaneous injections. Fecal excretion was slightly higher than urinary excretion after 11 weeks but corresponded to only about 1.6 percent of the daily dose. After 17 weeks the daily fecal excretion corresponded to 2.8 percent of the daily dose. After 23 and 29 weeks, when the urinary excretion of cadmium was greater, 11.2 and 6.6 percent, respectively, were found in the feces.

There is thus evidence that injected cadmium is excreted via some parts of the alimentary tract. On the other hand, the excretion is low, less than 5 percent during repeated exposure, as judged from experiments on rabbits. That both the gastric mucosa and intestinal mucosa excrete cadmium is clear, but as the parotic gland was shown by Berlin and Ullberg, 1963, to accumulate relatively large amounts and the pancreas has been shown in several of the reports to store large amounts of cadmium, it is conceivable that excretion from these two organs is important. The role of the bile has also to be taken into account. Berlin and Ullberg, 1963, found activity in the gallbladder after injection of ^{109}Cd as chloride to mice.

4.2.4.3 Excretion via hair

Truhaut and Boudene, 1954, found high concentrations of cadmium in hair from rats and rabbits injected with cadmium and suggested that hair analysis could be of value for determining cadmium levels in exposed workers. Berlin and Ullberg, 1963, found that cadmium accumulated in hair of mice given a single dose of ^{109}Cd.

Miller, Blackmon and Martin, 1968, found that the concentration in goat hair was about 20 percent of the concentration in the liver 15 days after a single oral dose of ^{109}Cd as chloride. After an intravenous dose the corresponding figure was about one percent. When this experiment was repeated by Miller et al., 1969, the concentrations in hair were only 3 percent of the concentrations in the liver. Nordberg and Nishiyama (to be published) found that in mice given a single intravenous injection of ^{109}Cd-chloride (4.5 mg Cd/kg), the decrease in cadmium levels in hair parallelled the decrease in whole body retention. Less than 0.5 percent of the total excretion between day 41 and 105 was excreted via the hair.

4.2.5 Biological half-life

After oral exposure to ^{109}Cd (intubation, compound not stated), Richmond, Findlay and London, 1966, estimated the biological half-life in female mice to be about 200 days. In figure 4:12 it can be seen that after a rapid clearance during the first five days, representing the passage of non-absorbed cadmium through the intestines, between 0.5 and 3 percent of the dose is retained. The retained amount will then decrease slowly during an observation period of nearly one year.

Cotzias, Borg and Selleck, 1961, gave mice ^{109}Cd as chloride (carrier free, 17 μCi) by intraperitoneal injection and determined whole body retention during 20 days. After 5 days about 95 percent of the injected dose remained and after 20 days, about 90 percent. The slow decrease during the latter part of the observation period indicates a half-life of at least 100 days.

After injection via the intraperitoneal or intravenous route, biological half-life was studied in female mice by Richmond, Findlay and London, 1966. They gave ^{109}Cd (compound and dose not stated) and made repeated determinations of whole body retention for periods of more than 400 days. After an initial rapid clearance during the first day, they estimated half-lives from about 40 days and increasing to 200-300 days during the latter part of the observation period. Other investigators (Eybl, Sýkora and Mertl, 1970, Nordberg and Nishiyama, to be published, and Tomita, personal communication) have studied whole body retention during 1-4 months after intravenous or subcutaneous injection of cadmium. From their data, it can be calculated that if the first rapid clearance is excluded, biological half-life in mice will vary between 25-100 days, generally confirming the findings of Cotzias, Berg and Selleck, 1961, and Richmond, Findlay and London, 1966, for that period of time.

In rats Durbin, Scott and Hamilton, 1957, estimated the biological half-life to be about 200 days after an intramuscular injection of ^{109}Cd (2 µCi per rat, compound not stated). They did not determine whole body retention, but determined cadmium in organs after 1, 8 and 64 days and estimated also the excretion via faeces and urine for 64 days. If an estimate is made using their data after 8 days compared with 64 days, thus eliminating the initial excretion phase, a biological half-life of about 300 days will be obtained.

Burch and Walsh, 1959, estimated that in dogs, it would take 260-500 days to eliminate 50 per cent of an intravenously injected dose of ^{115}Cd as nitrate. Also experiments on goats by Miller, Blackmon and Martin, 1968, indicate a long biological half-life of cadmium.

The explanation is not quite clear for the different half-lives obtained after injection in mice and rats during different time periods, but it is known that initially, cadmium will mainly be stored in the liver, and that during the first week, more cadmium will be excreted via the gastrointestinal tract than during the following weeks. Because cadmium will probably be bound to different proteins during this stage, it will take some time before a steady state is obtained. This is supported by the fact that blood levels of cadmium will increase during the first week (figure 4:5). Eventually blood and liver levels will decrease and renal levels of cadmium will increase. As the cadmium accumulated in the kidneys will not be noticeably excreted, this accumulation will prolong the biological half-life. This is illustrated by the results of Gunn and Gould, 1957, who found that 150 days after an intracardiac injection of ^{115}Cd as nitrate, the kidney was still accumulating cadmium.

The above mentioned values for biological half-lives of cadmium will only be valid before renal damage has occurred. If there is renal tubular dysfunction, the excretion of cadmium will increase and this might considerably change the biological half-life.

4.2.6 Cadmium metabolism in relation to zinc metabolism

It was mentioned in Chapter 3 that cadmium will appear together with zinc in nature and it could be expected that uptake of zinc could give rise to an uptake of cadmium. Zinc is an essential metal for animals and human beings (see e.g. Underwood, 1962, Bowen, 1966 and Schroeder et al., 1967) and zinc deficiency will give rise to disease, with symptoms from skin, gonads and hematopoietic system. As it was known that zinc deficiency in animals would give rise to effects on the gonads, Parízek, 1957, studied the influence of a simultaneous administration of zinc on the toxicity of cadmium. He found that in rats a large dose of zinc salt could prevent the action of cadmium on the testes (see also section 6:6). Similar findings have since been reported by Kar, Das and Mukerji, 1960, Gunn, Gould and Anderson, 1961, 1963a and b, Kar and Kamboj, 1964, Mason and Young, 1967, and Gunn, Gould and Anderson, 1968a and b. Not only the acute toxic effects of cadmium on the testes but also some long-term effects of cadmium may be prevented by simultaneous administration of zinc. Vigliani, 1969, gave rabbits injections of cadmium chloride for several months and found that the degree of proteinuria was less in rabbits treated with zinc. Powell et al., 1964, found that oral exposure to cadmium produced parakeratosis in calves similar to that caused by zinc deficiency. Petering, Johnson and Stemmer, 1969, reported that typical symptoms of zinc deficiency appeared in rats given a diet low in zinc and in rats given a sufficient amount of zinc and an equimolar amount of cadmium. Hill et al., 1963, Bunn and Matrone, 1966, and Banis et al., 1969, found that some of the effects of cadmium, especially anemia and weight loss, will be corrected by the administration of zinc in rats and mice.

Sporn et al., 1969, gave groups of rats 10 ppm cadmium, 80 ppm zinc and 10 ppm cadmium + 80 ppm zinc in food for 60 days. They determined the activities of 9 different enzymes in the liver. They found, for example, that cadmium caused decreased GOT-activity and that zinc given together with cadmium did not prevent this decrease. Cadmium caused a significant decrease in the oxidative phosphorylation in the liver mitochondria and zinc prevented this action of cadmium. Exposure to cadmium will tend to increase zinc levels in organs (Gunn, Gould and Anderson, 1962, Bunn and Matrone, 1966, and Banis et al., 1969). This is probably due to the greater burden placed upon zinc to counteract the action of cadmium. Part of this zinc will probably be found in metallothionein together with cadmium, as this protein will normally contain equimolar amounts of cadmium and zinc.

There is thus abundant evidence that cadmium and zinc oppose each other in animals. As many enzymes are zinc dependent, it is conceivable that part of the toxic action of cadmium will be caused by an exchange with zinc in some enzymes.

4.2.7 Influence of other compounds on the metabolism of cadmium

Kar, Das and Mukerji, 1960 and Mason and Young, 1967, found that selenium could protect the testes against damage by large doses of cadmium (see section 6.6). Gunn, Gould and Anderson, 1968a and b showed that though the uptake of cadmium in the testes increased after the administration of selenium dioxide, the testes were not damaged. Gunn, Gould and Anderson, 1968a, gave mice ^{109}Cd as chloride (1.4 mg/kg), s.c injection. One group was also given a subcutaneous injection of selenium dioxide. One hour after injection, the latter group had a blood level of cadmium 11 times higher than that of the group given cadmium alone. Organ distribution was also influenced. The group given selenium dioxide showed lower concentrations in liver and pancreas. There was no difference in kidney levels. Parízek et al., 1969, found a similar increase in blood levels of cadmium in rats given 2.2 mg Cd/kg and sodium selenite. Selenium given in the diet had a similar effect. Selenite was more effective than selenate. By separating plasma proteins by gel filtration they found a large amount of cadmium in macromolecular fraction in the selenite treated animals.

Injection of cysteine has also been shown to change the transport and distribution of cadmium. Gunn, Gould and Anderson, 1968a, found that cysteine prevented testicular damage by cadmium chloride in mice while kidney damage was made more prominent. One hour after a single injection of ^{109}Cd given simultaneously with cysteine, kidney levels of Cd were 30 times higher than in a group given Cd alone. At first the blood level of cadmium was also higher, but 7 days after injection, the cysteine treated animals had lower values than the group given Cd alone.

4.2.8 Discussion of mechanisms for transport, distribution and excretion

In this section, an attempt will be made to explain some of the mechanisms for transport, distribution and excretion of cadmium against the background of the data presented in the previous sections.

It is not known in what form cadmium is transported from the lungs, the intestines or injection sites to various organs. The studies by Perry and Erlanger, to be published, and Perry et al., 1970, showed that, in the first hours after intraperitoneal and intravenous injections, cadmium in blood was mainly in the plasma and partly dialyzable. This may mean that the initial uptake in the kidneys after injection is the result of glomerular filtration and reabsorption in the tubules of low molecular weight compounds. As will be discussed later, a similar mechanism probably holds true later when cadmium in plasma is bound to metallothionein.

There will be a rapid decrease in plasma levels of cadmium, whereas blood cell levels will decrease slowly. About 24 hours after injection cadmium in blood will be mainly in the cells. At that time there is a change in metabolism. Cadmium concentrations begin to increase in the red cells. In the liver cadmium appears in a low molecular weight protein fraction, probably metallothionein, the cadmium and zinc binding protein described by Kägi and Vallee in 1960 and 1961. The many unique properties of this protein are given in appendix 4:1. Metallothionein must play an important role for cadmium metabolism, both in normal and in chronically exposed animals, but as it probably does not exist in amounts large enough to handle injected doses in acute exposure, it will only to a minor degree be involved in the transport of cadmium during the first hours after injection.

After oral exposure only a relatively small percentage of the given dose is absorbed. The capability of the intestinal walls to produce metallothionein is not clear, but Starcher, 1969, has found a low molecular weight protein (m.w. around 10,000) in the duodenal mucosa of the chicken. This protein had the ability to bind copper and was thought to be important for the transport of this metal. Cadmium and zinc could displace the copper. A similar protein was found in the duodenal mucosa of the rat (Evans and Cornatzer, 1970) and in the duodenal mucosa of the bovine (Evans, Majors and Cornatzer, 1970). This protein might be identical with metallothionein. However, it is not clear whether it is synthesized in the duodenal mucosa or if it originates from the liver. Piscator, 1964, found large amounts of the protein in liver from exposed rabbits, but other organs might also contribute, as Lucis, Shaikh and Embil, 1970, found that human fibroblasts could produce a similar protein.

That pretreatment with small doses of cadmium will prevent some of the effects of a larger dose has been shown in several experiments (Terhaar et al., 1965, Ito and Sawauchi, 1966, the National Institute of Industrial Health, Tokyo, 1969, and Nordberg, Lind and Piscator, to be published). This finding is consistent with an induction of cadmium-binding protein by the small dose which can then bind a large cadmium dose.

Metallothionein is probably one of the proteins responsible for cadmium transport in the blood, but other proteins must also be involved. Carlson and Friberg, 1957, found that hemoglobin probably plays a role in cadmium metabolism. This was discussed by Piscator, 1963 and Axelsson and Piscator, 1966b, in connection with the finding that rabbits exposed to cadmium for longer periods of time developed hemolytic anemia, and that the release of cadmium-containing hemoglobin from the cells could be important for metabolism of cadmium.

As Carlson and Friberg, 1957, found that about one-third of the cadmium in hemolysate was dialyzable, cadmium could also be in a lower molecular weight form. Nordberg, Piscator and Nordberg (unpublished data) found that in mice exposed to 0.25 mg ^{109}Cd/kg by subcutaneous injection, part of erythrocyte cadmium was in a fraction, corresponding to metallothionein. As metallothionein has a molecular weight (about 7,000) low enough to permit it to enter the erythrocyte membrane, it could have entered the erythrocyte that way or could have been synthesized in the cells. In the plasma a small amount of cadmium was found both in high molecular and low molecular weight fractions, the latter corresponding to metallothionein.

It is thus possible for cadmium to appear in at least 3 forms: 1) bound to metallothionein, 2) bound to hemoglobin, and 3) bound to hemoglobin-haptoglobin. Then it can also be expected that albumin and zinc-dependent enzymes may bind it, probably depending upon the degree of exposure. By using a chelating agent (CaDTPA), Eybl, Sýkora and Mertl, 1966a, found that the bond of Cd to hemoglobin was weaker than that of Cd to albumin.

The selective accumulation in the kidneys has been thought to be due to reabsorption of metallothionein in the renal tubules (Piscator, 1964a and 1966c). The possibility that cadmium bound to hemoglobin released through hemolysis reaches the kidneys has been pointed out by Piscator and Axelsson, 1966b. As metallothionein is of low molecular weight, the small amount of free metallothionein in plasma can be expected to be cleared completely. As proteins in normal kidneys are almost completely reabsorbed, only trace amounts of the protein can be expected in the urine. When the kidney has become saturated with cadmium, the reabsorption decreases and tubular proteinuria appears (see section 6.1.2.3). If metallothionein is still filtered, less will be reabsorbed and it could be expected to appear in urine. Nordberg and Nordberg (unpublished data) have recently shown that this might happen. They found a low molecular weight protein fraction containing cadmium in urine from mice given injections of cadmium chloride for 5 months.

4.3 TRANSPORT, DISTRIBUTION AND EXCRETION OF CADMIUM IN "NORMAL" AND EXPOSED HUMAN BEINGS

In section 4:2 it has been shown that cadmium will be retained to a high degree in animals, especially in the kidneys and liver. Accumulation of cadmium in man is unavoidable, as even in non-polluted areas, cadmium will be found in food, air and water, often appearing together with zinc in the environment. For practical reasons, "normal" concentrations of cadmium are here defined as those found in human beings without known exposure to cadmium in industry or to excessive amounts in food, water and ambient air.

4.3.1 Transport and distribution in blood

Little is known about transport of cadmium in human beings but data from Lehnert (personal communication) indicate that more cadmium is in the plasma than in the cells in persons without known exposure to cadmium. He found a ratio between plasma and cell levels of 1.9 with a mean level in whole blood of 0.35 µg/100 ml (n = 18). Cadmium was determined by atomic absorption spectrophotometry after extraction.

As has been discussed in Chapter 2, it is difficult to determine accurately low concentrations of cadmium in biological material. Results from several investigations during the last ten years, in which methods such as neutron activation, atomic absorption spectrophotometry after extraction of metal, or spectrographic analysis with modern equipment have been used, have indicated that the average normal level, both in whole blood and in serum, is well below 1 µg/100 ml whole blood (see table 4:3). In these studies, there are still relatively large discrepancies among values reported by different authors. To what extent this reflects differences in analytical methods or in actual cadmium levels is not known.

Apart from those data listed in table 4:3, there are some reports in which considerably higher values have been stated. Butt et al., 1964, thus reported an average level of cadmium in whole blood of 209 μg/100 ml and in serum, 41 μg/100 ml. Mertz et al., 1968, reported average normal levels of 25 μg/100 ml in serum. They used spectrographic methods. It is not possible here to discuss the validity of their methods but it can be mentioned that the values are in the same range as the one reported by Friberg in 1952 and 1955 in the blood from rabbits given large doses of cadmium (^{115}Cd) by injections. The rabbits had symptoms of intoxication (see section 4.2.1.2). They are also considerably higher than the values given in table 4:3 for workers exposed in industry. In this report, the high values stated by Butt et al. and Mertz et al. are considered to be too high to be acceptable as valid data for human beings.

In exposed workers, Lehnert (personal communication) found more cadmium in cells than in plasma. At a mean blood level of 4.1 μg/100 ml, the ratio of plasma to cells was 0.5 (n=22) which is in accordance with the findings in animal experiments: cadmium will be bound mainly to the blood cells during exposure. In table 4:3 some data on cadmium concentrations in blood or serum of exposed workers are shown, but as exposure conditions are not fully known, they can only be used for demonstrating that cadmium concentrations in exposed workers are considerably higher than in "normals".

There will be fluctuations in blood levels of cadmium. Rogenfelt (personal communication) has determined cadmium concentrations 3-6 times a year for three years in blood of 20 workers exposed to cadmium oxide fumes in a Swedish factory producing a copper cadmium alloy. Production has varied to a large extent. When levels of cadmium in air have been measured, they have varied between 0.01-0.36 mg/m^3. In figure 4:13 it is seen that during exposure cadmium concentrations in blood from one worker varied between 5.3-9.1 μg/100 ml (spectrographic method, "normal" concentration $<$ 0.2 μg/100 ml). After the worker was removed from exposure, the cadmium levels slowly decreased. Nine months after exposure had ceased, the concentration in blood was still high, 3 μg/100 ml.

In some other workers, similar fluctuations were seen during exposure. In others, a more steady level was seen. It was not possible to relate cadmium concentrations to actual exposure or to duration of work.

Tsuchiya, 1969, determined cadmium in blood with an interval of one year in four workers exposed to cadmium oxide fumes. In two workers no change was seen, in one there was a decrease, and in another one there was an increase, so that the mean level for the group was about the same (19 μg/100 ml) at both determinations.

After exposure has ceased, blood concentrations of cadmium will usually decrease, as was illustrated in figure 4:13. Individual variations may exist. For example, Tsuchiya, 1969, reported a decrease from about 28 to 14 μg/100 ml in 1 year in 2 workers removed from exposure to cadmium oxide fumes. In a third worker removed from the exposure, there was no marked decrease. On both occasions, his blood concentrations were about 14 μg/100 ml. When this decrease does take place, it is slow. Piscator (unpublished data) found that in a group of workers, who had not been exposed for 20 years to cadmium oxide dust (this group included workers examined by Friberg, 1950), the mean cadmium concentration in blood was 0.9 µg/100 ml (n = 18; spectrographic method, "normal" concentration $<$ 0.2 µg/100 ml).

4.3.2 In organs

4.3.2.1 In liver and kidney

In contrast to blood, urine and hair, analysis of cadmium in liver and kidney from adult humans will give accurate results with most methods, as the concentrations usually are relatively high and thus interference from other compounds will be negligible. The basic work in this field has been done by Tipton, Schroeder, Perry and co-workers. In a series of papers, they presented normal values for cadmium and many other metals in organs of subjects from the United States and from other parts of the world, (Tipton and Cook 1963, Tipton 1960, Perry et al. 1961, Schroeder and Balassa 1961, Tipton et al. 1965, and Schroeder et al. 1967). During recent years, other investigators have also studied this problem (in Sweden: Piscator, 1964, and Piscator and Lind (unpublished data; in Germany: Geldmacher-v. Mallinckrodt and Opitz, 1968, and Henke, Sachs and Bohn, 1970; in Japan: Kitamura, Sumino and Kamatani, 1970, Ishizaki, Fukushima and Sakamoto, 1970b; in the United States: Morgan, 1969, and in the United Kingdom: Curry and Knott, 1970). Data on exposed workers have been reported by Friberg, 1950, 1957, Bonnell, 1955, Smith, Smith and McCall, 1960, Kazantzis et al., 1963 and Piscator (unpublished data).

As the tissue concentrations have been expressed in different ways, i.e., ppm wet weight, dry weight or ash, and as with regard to renal concentrations some authors have determined cadmium in whole kidney and some in renal cortex, conversion factors have been used. For liver, the ash values have been multiplied by 0.013 (Tipton and Cook, 1963) and the dry weight values have been multiplied by 0.29 to obtain wet weight values (Piscator, unpublished data). For kidney the ash values have been multiplied by 0.011 (Tipton and Cook, 1963) and the dry weight values by 0.21 (Piscator, unpublished data) to obtain wet weight values. Whole kidney values have been multiplied by 1.5 (Geldmacher-v. Mallinckrodt and Opitz, 1968) to obtain cortex concentrations.

As seen in some of the above mentioned papers, the ratio between kidney and liver concentrations in normal human beings is usually between 10 and 15 in the United States, the United Kingdom and Sweden, and between 5 and 10 in Japan. In exposed workers, on the other hand, considerably lower ratios have been seen, and sometimes liver levels have even exceeded kidney levels (Smith, Smith and McCall, 1960).

With regard to distribution within organs, Geldmacher v.-Mallinckrodt and Opitz, 1968, found at autopsy in 9 normal human beings a mean ratio of 2.2 (1.9-3.0) for cadmium in renal cortex to cadmium in medulla. Smith, Smith and McCall, 1960, found ratios of 1.1-1.4 in 3 controls. From the data of Ishizaki, Fukushima and Sakamoto, 1970b, and Kitamura, Sumino and Kamatani, 1970, it has been calculated that the ratios between cadmium concentrations in cortex and medulla were 2.3 (0.6-9.6) and 2.9 (1.3-6.3) in adults. In four exposed workers, who died 2-18 years after the last exposure, the ratios were 1.2-1.6 (Smith, Smith and McCall, 1960).

In figure 4:14 the data from investigations of cadmium in liver (ppm wet weight) in relation to age have been assembled for "normals" in different countries, occupationally exposed workers and Itai-itai patients. As can be seen, the values for "normals" in the United States, the United Kingdom and Sweden are comparatively low and the average values do not exceed 2 ppm wet weight. The normal values from two Japanese studies are considerably higher, particularly the values reported by Ishizaki, Fukushima and Sakamoto, 1970b, from the Kanazawa Prefecture, where the values are 5-10 times the values for the United States, the United Kingdom and Sweden. Kanazawa, regarded as having relatively low levels of cadmium in rice, is not included in the present investigation of areas in Japan suspected for pollution with cadmium. As the cadmium concentrations in the liver of the newborn are less than 0.002 ppm (section 4.1.3.2), it is obvious that there is an accumulation with age.

It should be pointed out that the Swedish and American investigations were based upon cases of sudden death, whereas in the British and two Japanese investigations, autopsies from hospitalized patients were used. In these materials, the basic disease and terminal illness will influence the results. Morgan, 1969, has shown that especially cancer will cause increased liver concentrations of cadmium (see Chapter 7). This factor, however, could only to a minor degree explain the higher levels in Japanese groups studied.

As can be seen, the liver values in figure 4:14 for the occupationally exposed workers and the Itai-itai patients are high, with no substantial observable difference. It is also noticeable that the upper level in "normals" from the Kanazawa Prefecture is within the range of the values in those occupationally exposed.

Of considerable importance is to what extent the values for the exposed workers can be regarded as representative for the actual values during exposure, as all of the workers included had been without exposure for a considerable time before death. In figure

4:15 the liver values have been plotted against the passage of time after the end of the exposure. In this figure the actual exposure times for the workers are given. Workers exposed to cadmium dust are separated from workers exposed to cadmium oxide fumes. As can be seen, there is no tendency for the liver values to decrease substantially with the time from the end of exposure in workers exposed to cadmium oxide dust. This would mean that the biological half-life in the liver of human beings subjected to this type of exposure is extremely long, as there is no evidence that those without exposure for only a short period had had a different exposure than those without exposure for a longer period. For cadmium oxide fumes there might be a tendency toward a faster clearance, but in summary, it can be said that the liver values, in any case for cadmium dust, in figure 4:15 should be fairly representative for the values during exposure, provided that the clearance during the very first year did not differ considerably from the later clearance.

In figure 4:16, values for renal cortex (ppm wet weight) in relation to age are given. It can be seen that the Swedish and British values are the lowest, but even these show a considerable accumulation with time. The values from the Kanazawa Prefecture are the highest among the "normals", with the other Japanese group and the American group in-between. Those occupationally exposed are scattered over a wide range, with about two-thirds of the values over 100 ppm and the rest between 20 and 100 ppm. The reason that the concentrations in some occupationally exposed workers and in the Itai-itai patients are even somewhat lower than in the "normals" is discussed in detail in sections 6.1.2 and 8.4.1.11. If renal damage is present, cadmium excretion will increase and renal levels of cadmium will decrease.

Figure 4:16 shows that cadmium has been accumulated with age in all groups studied, thus supporting the findings of Schroeder and Balassa in 1961. It will also be seen that after 50-60 years of age, a decrease in cadmium levels has taken place. At present, it is very difficult to explain this decrease. It might be connected with factors related to exposure or related to metabolic changes in kidneys or other organs in old age. The slight increase in urinary excretion of cadmium with age, described by Szadkowski, Schaller and Lehnert in 1969, supports the latter possibility (figure 4:17).

The transport to and metabolism of cadmium in renal cortex are closely related to zinc metabolism, as pointed out by Schroeder, 1967. Analysis of human renal cortex from 36 normal persons, aged 6-50 years, showed an equimolar increase in zinc content with increasing cadmium levels ($Zn = 1.13\ Cd + 2.33$) (Piscator and Lind, unpublished data). The basic level of zinc in the kidneys was not affected. The molar relationship between cadmium and zinc under normal circumstances is 1:1 in metallothionein, which is found in human kidneys (Pulido, Kägi and Vallee, 1966). It is possible that the equimolar relationship between increases in zinc and cadmium in normal renal cortex reflects the metallothionein content.

4.3.2.2 Other organs

In the pancreas the levels of cadmium in "normals" are usually below 2 ppm wet weight. Tipton and Cook in 1963 found a median value of about 1 ppm in U.S. citizens, whereas Tipton et al. in 1965 found a median value of 2.8 ppm wet weight in subjects from the Far East. None of the presently available data has related cadmium in pancreas to age. In exposed workers, 39-80 ppm wet weight have been recorded by Friberg in 1957 and Smith, Smith and McCall in 1960, and in Itai-itai patients, 45-65 ppm, by Ishizaki, Fukushima and Sakamoto in 1970b.

"Normal" concentrations of cadmium in the lungs have been reported by Tipton and Shafer in 1964. In subjects from San Francisco, they found a mean level of 0.34 ppm wet weight. Molokhia and Smith in 1967 found in 21 Scottish subjects (40-70 years old) a mean level of 0.26 ppm wet weight and Smith, Smith and McCall in 1960 found in 3 British subjects (mean age: 54) a mean level of 0.71 ppm wet weight. In Germany Geldmacher-v. Mallinckrodt and Opitz in 1968 found a mean level of 0.11 ppm wet weight in subjects who were 3-62 years of age. Cadmium levels in the lungs seem to increase with age. In most other organs cadmium will be found, as Tipton and Cook, 1963, and Smith, Smith and McCall, 1960, have attested, but there are not enough data on accumulation with regard to age to draw any conclusions. Concerning cadmium concentrations in other organs, it can be mentioned that Smith, Smith and McCall in 1960 and Friberg in 1957 found relatively large concentrations of cadmium (25-83 ppm wet weight) in the thyroid in cases of chronic cadmium poisoning. In bone, cadmium levels normally are low, below 1 ppm with accumulation with age, as found by Kitamura, Sumino and Kamatani, 1970.

4.3.3 Excretion

4.3.3.1 Urinary excretion

Also with regard to urine there have sometimes been big differences in reported normal concentrations, but most reports during the last ten years have stated an average normal excretion of less than 5 µg/day, and in most studies, 1-2 µg/day (table 4:4). In some reports, such as those by Schroeder et al., 1967, and by Tipton and Stewart, 1970, considerably higher figures have been given, which can not be accepted. In some European countries and in the United States, the daily intake of cadmium is less than 50 μg (see Chapter 3). Even if a calculation is based on as high an absorption as 10 percent in the alimentary tract, it will be seen that less than 5 μg/day will be absorbed. We can not thus expect more than a few micrograms to be excreted via the urine every day. There seems to be a slight increase with age, as shown by Szadkowski, Schaller and Lehnert, 1969, but even in people around 60 years of age, cadmium excretion is still very low, as illustrated in figure 4:17.

Cadmium excretion in exposed workers has been extensively studied and documented by Truhaut and Boudene, 1954, Bonnell, 1955, Smith, Kench and Lane, 1955, Smith and Kench, 1957, Kazantzis et al.,1963, Suzuki, Suzuki and Ashizawa, 1965, Tsuchiya, 1967 and 1969, Adams, Harrison and Scott, 1969, and Lehnert et al., 1969. It will be seen in table 4:5 that during exposure, cadmium excretion will vary from near zero to around 1 mg/day.

In several of the above mentioned reports it will be seen that exposure to cadmium has taken place without resulting in an increase in urinary excretion of cadmium. Tsuchiya, 1967, found that workers exposed to cadmium oxide fumes, about 0.1 μg/m^3, for less than one year, did not excrete more cadmium than controls. In 1969 he found that blood levels varied between 1 and 10 μg/100 ml in a group of 20 workers in an alkaline battery factory, indicating that cadmium had been absorbed and accumulated. In two of these workers, urinary excretion of cadmium was 1 μg/l, i.e., within normal limits.

Adams, Harrison and Scott, 1969, determined urinary cadmium in 75 workers in different departments in an alkaline battery factory. In the assembly department, where cadmium concentrations in air had been measured at around 0.1 mg/m^3 since 1957 and in in the plate-making department, where concentrations of cadmium in air had varied between 0.1 and 0.5 mg/m^3, 9 out of 51 men excreted less than 2 µg/l. Ten workers had proteinuria and excreted 30-170 µg/l. The workers without increased excretion of cadmium had thus been exposed for several years to cadmium concentrations known to cause considerable accumulation of cadmium. They had no proteinuria, and it is conceivable that their renal levels of cadmium had not yet reached the point at which renal damage occurs and cadmium excretion begins. That during exposure excessive amounts of cadmium may be absorbed without an increase in excretion of cadmium is in accordance with the findings in animal experiments described in section 4.2.4.1.

An increase in cadmium excretion has been reported in workers without detected proteinuria by Smith and Kench, 1957, and Adams, Harrison and Scott, 1969, but it should be remembered that for the determination of cadmium, quantitative methods were used, whereas semiquantitative methods were used for the determination of urinary protein.

When proteinuria is present, there is always an increase in the excretion of cadmium, which is also in accordance with the results from animal experiments (section 4.2.4.1). It has not been possible to relate excretion of cadmium to excretion of protein (Smith, Kench and Lane, 1955, and Smith and Kench, 1957).

After exposure has ceased, cadmium excretion will decrease, whereas proteinuria will persist (see also section 6.1.2.1.1). Adams, Harrison and Scott, 1969, found that in a group of workers under exposure and with proteinuria, the mean excretion of cadmium was 94 µg/l, whereas in a group of retired workers (not exposed for 0.5-5 years) with proteinuria, the mean concentration of cadmium in urine was 28 µg/l.

Tsuchiya, 1969, determined urinary cadmium in three workers at the time they were removed from exposure to cadmium and one year later. In one worker there was a decrease from about 250 to 125 μg/l, whereas in the other two workers, cadmium excretion was at both times about 100 μg/l.

Bonnell, Kazantzis and King, 1959, found that urinary excretion of cadmium could be affected by general health. Acute illnesses, such as pneumothorax and pneumonia caused considerable increases in excretion of cadmium. Terminal illnesses will also increase excretion as pointed out by Smith, Smith and McCall, 1960.

The relationship between cadmium excretion and zinc metabolism has been illustrated by the findings of Suzuki, Suzuki and Ashizawa, 1965. They observed a decrease in the excretion of zinc with an increasing excretion of cadmium.

4.3.3.2 Fecal excretion

Fecal excretion of cadmium has been determined in normal human beings by Essing et al., 1969, who found a mean level of 16 μg/100 g (n = 23). They estimated the daily amount in feces to be 31 μg. Tipton and Stewart, 1970, found a mean amount of 42 μg/day in 3 persons in a long-term balance study. Tsuchiya, 1969, found a mean daily amount of 57 μg in feces from 4 Japanese men. No known excessive exposure was stated. It is not known how much cadmium will come from cadmium not absorbed from food and how much will have been excreted via the intestines. It is also not known if cadmium excreted into the gastrointestinal tract will be reabsorbed. Data from injection experiments on animals suggest that only a few percent of the absorbed cadmium will be excreted via feces.

4.3.3.3 Excretion via hair

During the last years, the possibility of using hair as an indicator of exposure has been investigated, as seen in table 4:6.

Analysis of metals in hair is difficult, as external contamination both from dust and from metals in hair lotions, hair sprays, etc., must be taken in account.

In the study by Schroeder and Nason, 1969, the influences of sex, age and color of hair on the levels of cadmium in hair were investigated. They found that male black hair contained less cadmium than brown, blonde or red hair. In women, grey hair contained less cadmium than hair with natural color. Their data indicate that cadmium levels in hair are higher in the particular area investigated (Brattleboro, Vermont) than in Stockholm, Sweden, and can be consistent with the fact that organ levels of cadmium seem to be higher in the United States than in Europe.

Ishizaki, Fukushima and Sakamoto, 1969, determined cadmium in hair from men and women, above 55 years of age, from the endemic district of the Itai-itai disease. They found mean concentrations of about 0.4 and 0.7 ppm, respectively. There were, however, no controls for the men. There were only 3 controls for the women and they had a mean concentration in hair of about 0.4 ppm.

Hammer et al., 1970, investigated 10 year-old children living in areas with varying degrees of pollution. They found good agreement between exposure levels and hair levels of cadmium.

In exposed workers, hair analysis will be of little value, as external contamination will be great. Analysis of metals in hair is a relatively new field. More information is needed about the chemistry of hair, pre-analysis treatment and significance of levels in hair in relation to organ levels before the value of cadmium analysis of hair can be ascertained.

4.3.4 Total body burden and renal burden.

A "standard American" of 70 kg and about 50 years of age has accumulated about 30 mg of cadmium as estimated by Schroeder and Balassa, 1961, and Schroeder et al., 1967, using the data by Tipton and Cook, 1963, on cadmium concentrations in human tissues. About one third of the cadmium is in the kidneys and about 15 percent in the liver. About half of the total body burden of cadmium will thus be found in liver and kidneys together.

Apart from the abovementioned data there is only one report based on actual findings from which it is possible to get an estimate of total body burden in normal human beings. Smith, Smith and McCall, 1960, determined cadmium in organs from 3 men about 50 years of age without known exposure to cadmium. Analysis was made of liver, kidney, skin, muscle, stomach, colon, heart etc. From their data the following mean amounts of cadmium in different organs can be calculated. Liver: 3.9 mg, Kidney: 4.1 mg, Muscle: 3.3 mg, Skin: 0.4 mg, Stomach and Colon: 0.6 mg.[x]. Those make a total of 14.5 mg, and the renal percentage of total cadmium was about 28 percent. About 55 percent of total body burden was in kidneys and liver together.

Using the above-mentioned estimate, that half of the body burden is in liver and kidneys, a corresponding "standard man" in the United Kingdom and Sweden would accumulate about 15-20 mg of cadmium. This estimation is based on data on concentration of cadmium in liver and kidney by Curry and Knott, 1970, Piscator and Linc to be published and Piscator, unpublished data, and on an assumption of average liver and kidney weights of 1,700 and 300 grams, respectively. Similar estimates based on the data from Kanazawa in Japan (Ishizaki, Fukushima and Sakamoto, 1970) will give an

[x] Lung: 0.7 mg. Bone marrow: 0.5 mg. Other organs: About 1 mg.

average total body burden of about 80 mg in a Japanese person of 70 kg and 50 years of age in that area. If data from Kobe, Japan, are used instead (Kitamura, personal communication), the average body burden will be lower, about 40 mg. It should be remembered, however, that body weights and thus also organ weights in Japan are lower than in Europe and the United States.

If organ values are to be used to calculate total body burden in human beings during exposure to large concentrations of cadmium via inhalation or ingestion, the above mentioned proportions can not be used. During or immediately after exposure, but before renal damage has occurred with increased excretion of cadmium, the liver contains considerably more cadmium than the kidneys. This is shown by the animal experiments of Decker et al., 1958.

Animal experiments have further shown that during repeated exposure about 75 percent of the total administered dose will be found in liver and kidneys before renal damage occurs (Friberg, 1952, and Axelsson and Piscator, 1966a). As excretion during that period will be only a few percent of the dose, the amount of cadmium in liver and kidney will be about 75 percent of the total body burden. The main part will be in the liver and only 5-10 percent of the total body burden will be in the kidneys.

There is no reason that human beings should differ much from animals in this respect. For calculating the total body burden in a worker during exposure before renal damage has occurred, it can thus be assumed that the amount of cadmium in liver and kidneys together will be about 75 percent of the total body burden. The same would probably hold true for people exposed to excessive amounts of cadmium via the peroral route.

With regard to body burden in workers several years after exposure, only the data by Smith, Smith and McCall, 1960, lend themselves to a calculation of total body burden. They determined cadmium in most organs, including muscle, skin and fat. In three workers with slight renal dysfunction, autopsied 5-10 years after the last exposure, it was estimated that between 40 and 70 percent of the total cadmium accumulation was in liver and kidneys together, about 10 percent in the kidneys.

In figures 4:14 and 4:16 liver and renal concentrations of cadmium at autopsy of exposed workers are shown (see also table 6:1). With assumed liver and kidney weights of 1,700 and 300 grams, respectively, the total amount of cadmium in these workers in liver and kidney would have been between 50 and 600 mg. With 50 percent of the cadmium in liver and kidneys, the total body burden at time of death would have been 100-1,200 mg. Total body burden at the time exposure ceased must have been higher as excretion of cadmium due to renal disease must have caused losses of cadmium.

Of special interest is the percentage in the kidneys of the total body burden of cadmium, as such data are necessary for a later discussion (see section 6.1.2.4), with regard to intake of cadmium and critical levels in kidney. In normal human beings the kidney contains about one-third of the total cadmium, whereas in workers exposed to high concentrations of cadmium oxide fumes for less than 10 years and with sufficient renal cortex concentrations of cadmium (about 300 ppm) to have caused slight renal damage, about 10 percent of the total body burden has been found in the kidneys. It could thus be suspected that the percentage of renal cadmium decreases with increasing renal concentrations. Data from investigations in the United States (Schroeder and Balassa, 1961) and in Sweden (Piscator, unpublished data) show that in people 20-59 years of age the ratios between cadmium concentrations in liver and renal cortex are about

0.06 at a mean concentration of 20 and 30 ppm, respectively. Corresponding calculations based on the data by Ishizaki, Fukushima and Sakamoto, 1970b, and Kitamura, Sumino and Kamatani, 1970, in Japan give ratios of about 0.11 at mean renal cortex concentrations of about 42 and 87 ppm, respectively. There could thus be a slight tendency for an increase in ratio with increasing renal concentrations, but it should be remembered that the U.S. and Swedish data were obtained by analysis of cases of sudden death, whereas the Japanese results were from investigations of hospitalized patients who died from severe diseases, which might have changed the ratios. To obtain a more homogenous material covering a large concentration range, cadmium has been determined in liver and kidney cortex of slaughtered horses mainly between 10 and 20 years of age and without known disease (Piscator, unpublished data). In figure 4:18 it will be seen that there is no change in ratio with increasing renal concentrations, even as high as 100-250 ppm. It can thus be assumed that during prolonged exposure to relatively small amounts of cadmium and before renal dysfunction has appeared, the relative amount of cadmium in the kidneys will be about the same at both high and low renal concentrations of cadmium.

In summary it can be stated that in a "standard man" about 50 percent of the total body burden is in liver and kidneys. The total body burden in a "standard man" in the United States is probably about 30 mg of cadmium. The corresponding values for the United Kingdom and Sweden are probably about 15-20 mg. In Japan the total body burden is considerably higher, in one area (considered not to have an excessive exposure to cadmium) it could be estimated to be about 80 mg.

For workers during exposure to cadmium, a higher percentage of the total body burden is probably in the liver and kidneys. Animal experiments indicate about 75 percent before renal damage occurs. Considerable time after cessation of exposure and when renal damage is evident, the total amount of cadmium in the liver and kidneys is lower, probably around 50 percent of the total body burden. In autopsies of workers with exposure to cadmium and with signs of intoxication, total body burdens of 100-1,200 mg of cadmium have been estimated. Total body burden at the time exposure ceased must have been higher, as excretion of cadmium due to renal disease must have caused losses of cadmium. During prolonged exposure to small amounts of cadmium and before renal dysfunction has appeared, renal cadmium will constitute about one-third of the total body burden.

4.4 RELATIONSHIPS AMONG CONCENTRATIONS OF CADMIUM IN BLOOD, URINE AND ORGANS

As it is of great importance to know to what extent determination of cadmium in blood or urine may be of assistance in making an estimate of cadmium concentrations in organs and total body burden, this question will be discussed in the following sections.

4.4.1 Relationship between concentrations of cadmium in blood and organs

4.4.1.1 In animals

As mentioned in section 4.2.1.1, the concentration of cadmium in the blood of experimental animals given a single injection of the metal salt displays a two-phase course during the first two days after injection. As this course is not reflected in other organs, it is evident that blood values do not depict the situation in any body organs during this first period. Even if the elimination phase counted from the second maximum seems to be slower, available data indicate that it is considerably faster than the elimination, both from whole body and critical organs. However, more data on these relationships are necessary before any definite conclusions can be drawn.

Data from repeated exposure are scarce. Most of the available evidence is from Friberg, 1952 and 1955, and show that blood concentrations increase continuously during continuous exposure to cadmium - but only to a certain level. No estimations of blood/organ concentrations or blood/whole body concentrations are available for different exposure levels.There also are no data which elucidate to what extent fluctuations in exposure are reflected in fluctuations in blood and organ concentrations.

4.4.1.2 In human beings

The data which have been presented do show that blood levels of cadmium in exposed workers might be considerably higher than in people without known exposure to cadmium. There will be fluctuations in blood levels of cadmium, possibly reflecting fluctuations in recent exposure.

In a Swedish factory it was found (Piscator, unpublished data) that amoung a group of 7 carpenters and repairmen who had been employed for more than 20 years but not directly exposed to cadmium, two men had renal damage at blood levels of 2.1 and 3.1 µg/100 ml blood, whereas two workers in the cadmium department with 3-4 years exposure had cadmium concentrations in blood of 4.8 and 5.8 µg/100 ml blood without any renal damage. A low value for cadmium in blood thus does not exclude a considerable accumulation in the kidneys and a high value does not necessarily mean that renal damage has occurred.

Piscator (unpublished data) found that in a group of workers not exposed for 20 years, urinary excretion of protein was related to cadmium concentrations in blood (figure 4:19). It had earlier been shown (Piscator, 1962a) that in these workers proteinuria was related to exposure time, i.e., the larger the absorbed and accumulated amount, the greater the renal dysfunction. That a correlation could be found between cadmium in blood and proteinuria indicates that the blood levels reflected organ levels in these workers when they were without exposure for several years.

.4.2 Relationship between concentrations of cadmium in urine and organ or blood concentrations

4.4.2.1 In animals

After a single injection of cadmium, not more than a few percent will be excreted during the first weeks. During that period levels of cadmium in blood will both increase and decrease. Liver concentrations will slowly decrease and renal levels will increase. Urinary excretion of cadmium is not related to any of the above mentioned changes in blood or organ concentrations. After repeated exposure urinary excretion will be low for long periods of time, during which levels in blood and organs will increase continuously. A low concentration of cadmium in urine can thus be associated with both high and low concentrations of cadmium in organs or in blood.

The simultaneous occurrence of proteinuria and increased excretion of cadmium as shown by Friberg, 1952 and Axelsson and Piscator, 1966a, indicate there is a common mechanism for the two parameters. Proteinuria during exposure to cadmium is a sign of renal tubular dysfunction (see section 6.1.2.3).

Axelsson and Piscator, 1966b, found also that whereas there was no association between renal levels of cadmium and urinary excretion of cadmium in rabbits subjected to repeated exposure, there were significant negative correlations between excretion of cadmium and renal tubular capacity to reabsorb glucose and renal activity of alkaline phosphatase. These results and the relationship between proteinuria and cadmium excretion indicate that once cadmium starts being excreted, the amount excreted will reflect more the functional state of the kidney. Thus, the cadmium excretion in itself will be a measure of renal function during exposure rather than a measure of organ concentrations. The mechanisms for this will be further discussed in section 6.1.2.3.

4.4.2.2 In human beings

Cadmium will accumulate in liver and kidneys from birth up to 50 years of age. Whereas the newborn has only about 1 μg or less in his body, the "normal" adult may have a total body burden of about 30 mg. With increase in age, there seems to be a slight increase in cadmium excretion. Urinary excretion of cadmium is very low all of the time, however, usually less than 2 µg/day. It is at present not possible to say if this increase parallels the increase in renal levels.

The findings in exposed workers confirm the findings in animal experiments. During a considerable time, the length of which depends on exposure conditions, urinary excretion of cadmium will be within normal levels. When renal damage with proteinuria and other functional abnormalities occurs, there will also be increased excretion of cadmium (see section 4.3.3.1).

Tsuchiya (1969) determined cadmium in blood and in urine in three groups of workers. One control group (n = 9) in an alloy factory, not directly exposed to cadmium, one group (n = 11) exposed to cadmium oxide fumes in the alloy factory, and one group (n = 20) in an alkaline accumulator factory exposed to cadmium oxide dust were examined. In the control group and in the group exposed to cadmium oxide dust, blood concentrations of cadmium varied between 0.2 and 4 µg/100 ml and between 3 and 7 µg/100 ml, respectively. Corresponding values for urinary excretion were 2-10 and 1-40 µg/l. In these two groups there were no correlations between cadmium concentrations in urine and blood. In the group exposed to cadmium oxide fume, blood levels were between 10-35 µg/100 ml and urinary cadmium between 10-230 µg/l. As all workers showed an increase in cadmium excretion, it is conceivable that all had renal dysfunction. In that group a correlation ($p < 0.05$) was found between blood levels and urinary levels of cadmium.

Tsuchiya's data thus show no uniform findings in the three groups with regard to relationships between blood levels and urine levels.

High levels of cadmium in blood may be combined with low urinary concentrations of cadmium.

4.4.3 Conclusions

There are thus no data which show that concentrations of cadmium in blood or urine can be used for estimating organ levels of cadmium in human beings. It cannot be recommended that any fixed level in blood or urine can be used for control of exposed workers or populations exposed to cadmium in food or ambient air. Concentrations of cadmium in urine above "normal" would indicate that signs of cadmium induced renal dysfunction had already occurred, provided other reasons for the increased excretion could not be demonstrated.

4.5 GENERAL CONCLUSIONS ON METABOLISM

4.5.1. In animals

The fate of cadmium in experimental animals has been studied after exposure via the respiratory, gastrointestinal or injection routes. Absorption rates are not known exactly with regard to inhaled or ingested cadmium, but reasonable estimates are about 10-40 and 2 percent, respectively. The absorption of ingested cadmium may increase considerably if the diet is deficient in calcium and/or protein. There are also considerable individual variations.

In blood, cadmium has been studied after single and repeated injections. After a single injection cadmium will initially be mainly in the plasma, but during the first 24 hours after injection, a rapid clearance from plasma takes place, so that eventually the concentration in the cells will exceed that in the plasma.

After repeated exposure cadmium will mainly be found in the blood cells, bound to proteins, such as metallothionein and hemoglobin. During continuous exposure to cadmium, there will be a continuous increase in blood levels of cadmium, but at a certain level, a plateau will be reached and no further increase will be seen. When exposure has ceased, the concentration in blood will decrease.

About 75 percent of the cadmium will be found in liver and kidneys together before the occurrence of some renal damage. Immediately after single exposure, the main part will be in the liver, but eventually renal levels will exceed liver levels. Repeated exposure to small amounts will also result in the renal concentrations surpassing the liver concentrations, but with increasing doses, liver concentrations will exceed renal concentrations.

In the kidney the highest concentrations of cadmium will be found in the cortex. It is possible that it is transported to the cortex with metallothionein. During exposure there will be a continuous accumulation of cadmium in the kidneys and urinary excretion of cadmium will be low. When the cadmium level in the kidneys reaches about 200-300 ppm wet weight (or about 400 ppm wet weight in the cortex), there will be no further increase and urinary excretion of cadmium will increase considerably. As proteinuria occurs at this time, this change in metabolism is thought to be due to the renal tubular dysfunction. Whereas before renal damage has appeared, the total excretion via urine, feces and other routes will be less than 10 percent of the daily administered dose, daily excretion may exceed the daily dose after renal damage has appeared.

The biological half-life of cadmium after single oral exposure has been estimated to be about 200 days in mice. After single intramuscular injection the half-life has been estimated to be about 200 days in rats. If the initial clearance during the first week is not taken into account, the half-life can be estimated to be 300 days. After single intravenous injection a half-life of about 400 days has been estimated in dogs, including the initial clearance.

The metabolism of cadmium is intimately connected with zinc metabolism. The low molecular weight protein, metallothionein, is able to bind both cadmium and zinc, and these two metals will thus be transported together. Zinc is an essential metal and many enzymes are zinc-dependent. Cadmium seems to have the ability to exchange with zinc and thus cause changes in enzymatic activity. During exposure to cadmium, organ levels of zinc will increase.

4.5.2 In human beings

Cadmium may be absorbed after ingestion or inhalation of cadmium compounds, but there are no experimental data at present that allow any conclusions to be drawn with regard to absorption rates in human beings. Estimations starting from body burdens found at autopsies together with estimated intake of cadmium in the past point, however, to an average absorption via the oral route of somewhere between 3 and 8 percent. Based on the animal data, an absorption rate of about 10 percent of ingested cadmium must be considered quite possible in individual cases, under certain circumstances such as calcium and protein deficiency.

The newborn contains less than 1 µg of cadmium, indicating that the placenta is an effective barrier to cadmium.

Normal concentrations of cadmium in blood will be well below 1 µg/100 ml blood. In exposed workers considerably higher values have been reported, usually between 1 and 10 µg/100 ml. In exposed workers cadmium will be found mainly in the blood cells. After exposure has ceased, concentrations of cadmium in blood will decrease slowly.

In normal human beings the largest concentrations of cadmium will be found in the kidneys. This accumulation in the kidneys reaches its maximum when a person is around 50 years of age, when mean concentrations in the renal cortex have been shown to be 20-50 ppm wet weight in persons living in the United Kingdom, the United States and Sweden. In older persons, lower values are seen. In two areas in Japan, mean normal levels of around 50 and 90 ppm, respectively, have been found in the cortex.

In exposed workers concentrations of around 300 ppm have been found in the cortex, but values within the normal range have also been reported despite signs of cadmium intoxication. Losses of cadmium, due to renal dysfunction, are thought to be the cause of these low values.

In normal human beings in the United Kingdom, Sweden and the United States, the concentration in the kidneys is often 10-15 times higher than that in the liver. and in normal Japanese persons, 5-10 times higher, whereas in workers exposed to cadmium, the ratio is still smaller and in some cases liver concentrations of cadmium have exceeded the renal levels. The pancreas may contain high concentrations of cadmium.

As in animals, cadmium metabolism in humans will be intimately related to zinc metabolism. When cadmium is accumulated in the kidneys, there will be a corresponding molar increase in renal concentrations of zinc. The cadmium and zinc-binding protein, metallothionein, has been found in normal human kidneys and metallothionein probably plays an important role in the metabolism of cadmium in human beings.

In normal human beings, the excretion of cadmium via the urine is very low, around 2 μg/day or less. There is a slight increase in excretion with age. It is not known to what extent excretion via the gastrointestinal tract plays a role for the human metabolism of cadmium, but if the human being reacts in the same way as animals, less than 5 percent of an absorbed dose can be expected to be excreted via feces. Small amounts of cadmium might also be excreted via hair, skin, sweat, etc., but the total excretion will probably be much less than 10 percent of an absorbed dose.

During occupational exposure to cadmium, a worker's excretion of cadmium via urine might for some time be within normal limits, but sooner or later it will increase considerably. Proteinuria in cadmium workers is always combined with increased excretion of cadmium during exposure, indicating that renal tubular dysfunction plays a role in the increased excretion. After exposure has ceased, less cadmium will be excreted, but the normal level will not be reached.

Available data do not lend themselves to an estimate of the biological half-life of cadmium in man, but as the biological half-life in such small animals as mice and rats is 200 days or more, it is conceivable that cadmium will be retained for many years in man once it has been absorbed. This is supported by findings in autopsies of workers which indicate a very slow decrease in liver levels after exposure ceased. Renal damage will change the metabolism of cadmium and shorten the half-life.

As cadmium concentrations in blood during exposure will vary independently of renal concentrations of cadmium, the determination of cadmium in blood will be of limited assistance for making an estimate of renal concentrations.

The determination of cadmium in urine will not be of any value in investigations of suspected renal accumulation, as during the period of accumulation before the occurrence of renal damage, cadmium excretion will be within normal limits. Concentrations of cadmium above "normal" would indicate that signs of renal-induced dysfunction are already present, provided other reasons for the increased excretion could not be demonstrated.

APPENDIX 4:1

METALLOTHIONEIN: OCCURRENCE AND PROPERTIES

In 1957 Margoshes and Vallee reported that equine renal cortex possessed a cadmium-containing protein of low molecular weight. Further work by Kägi and Vallee, 1960 and 1961, resulted in the purification of a protein with a molecular weight around 10,000, which they named metallothionein becuase of its high content of metals, such as cadmium and zinc, and of sulphur.

This protein had many unique properties. In contrast to most other proteins, metallothionein absorbed UV-light of a wavelength of 250 nm, but not of 280 nm. The absence of amino acids, suggested by the lack of absorption at 280 nm, was verified by amino acid analysis. The absorption at 250 nm was shown to be dependent on the cadmium-mercaptide bond by the following procedure: The protein was dialyzed at a low pH or against EDTA whereby a metal free protein, thionein, was obtained. Thionein did not have any absorption at 250 nm because the cadmium mercaptide bond had disappeared. Addition of cadmium or zinc to thionein gave cadmiumthionein and zincthionein, respectively. By such addition the cadmium mercaptide bond was reestablished in the cadmium thionein and the absorption at 250 nm reappeared.

The amino acid analysis showed that the high sulphur content, about 9 percent, was due to a very high percentage of cysteine in the protein. In metallothionein obtained from horse kidney, the cadmium content was 5.9 percent and the zinc content, about 2.2 percent.

Proteins almost identical with metallothionein from horse kidney have been isolated and characterized from the liver of cadmium exposed rabbits (Piscator, 1964, Kägi and Piscator, to be published, and Nordberg et al., to be published), and from human renal cortex (Pulido, Kägi and Vallee, 1966). Also from the liver of horses a protein has been isolated which is identical with horse kidney metallothionein in its amino acid composition and in several other characteristics, but which has mainly zinc bound to it (Kägi, 1970). Zinc constituted more than 90 percent of the total metal content of this "hepatic metallothionein" which contained 11 percent sulphur, corresponding to 33 percent of thionein made up by cysteine. The molecular weight was estimated to be about 6,600, i.e., lower than earlier mentioned values. The ratio of cysteinyl residues to zinc was 3 and Kägi suggested that a negatively charged complex had been formed $[Zn\ (Cys)_3]$.

In addition to the studies mentioned above, there are some other reports of similar proteins in organs from other animals, i.e., cadmium exposed rats and mice (Shaikh and Lucis, 1969, Nordberg, Piscator and Lind, to be published) in,the rat liver and kidney (Wisniewska-Knypl and Jablonska, 1970 , in the duodenum of the chicken (Starcher, 1969), of the rat (Evans and Cornatzer, 1970) and of the bovine (Evans, Majors and Cornatzer, 1970).

Metals other than cadmium and zinc can be bound by metallothionein. Pulido, Kägi and Vallee, 1966, found that renal metallothionein from human beings treated with mercurial diuretics contained mercury. By experiments with equine metallothionein, Kägi and Vallee, 1961, showed that the bond between metallothionein and mercury was stronger than the one to cadmium, which in turn is about 3,000times stronger than the one to zinc. Jabubowski, Piotrowski and Trojanowska, 1970, found that part of the renal mercury from rats injected with $^{203}HgCl_2$ was in a low molecular weight protein, which had characteristics in common with metallothionein.

A protein similar to metallothionein but containing mainly copper was found in duodenum of different species (Starcher, 1969, and Evans, Majors and Cornatzer, 1970). Both zinc and cadmium, however, could displace the copper bound to this protein.

It is not known to what extent the above mentioned proteins which bind the different metals are identical, but all contained a lot of metal and were of low molecular weight. Thus it is highly probable that they play an important role for the absorption, transport and excretion of metals, especially cadmium. It is of interest in this connection that a low molecular weight substance, possibly metallothionein, binds an important part of cadmium in blood of mice exposed to this metal (Nordberg, Piscator and Nordberg, unpublished data).

The importance of metallothionein for absorption, transport, excretion and toxicity of cadmium has been discussed elsewhere in this report (section 4.2.1) and will not be dealt with further here.

Table 4:1 CONCENTRATION OF 1) CADMIUM IN RENAL CORTEX AND LIVER AND 2) INORGANIC MATTER IN PERCENT OF WET WEIGHT OF THE RIGHT TIBIA[x] (from Larsson and Piscator, to be published).

		Cd µg/g dry weight mean and standard deviation		Inorganic matter percent of wet weight mean and standard deviation
Group	n	Renal Cortex	Liver	Right tibia
Cd + Ca	6	136±23	29±5	47.67±0.83
Cd - Ca	6	205±23	49±6	44.40±0.52
- Ca	6	< 5	<1.5	47.12±0.58
Controls	6	< 5	<1.5	48.01±1.20

[x] Rats were treated for two months with cadmium and normal diet (Cd + Ca), cadmium and calcium deficient diet (Cd - Ca), calcium deficient diet (- Ca) and normal diet (controls). Cadmium was given as 25 ppm in the drinking water to the cadmium exposed groups.

Table 4:2 RATIOS BETWEEN CADMIUM CONCENTRATIONS IN LIVER AND KIDNEYS IN RATS AND DOGS IN RELATION TO EXPOSURE LEVEL (data from Decker et al., 1958, and Anwar et al., 1961).

	Ratio liver Cd/renal Cd		
	Rats		Dogs
µg Cd/ml H_2O	6 months	12 months	4 years
0.1	-	0.14	-
0.5	0.20	0.19	0.17
2.5	0.38	0.24	0.19
5.0	0.43	0.31	0.24
10.0	0.67	0.47	0.30

Table 4:3 CADMIUM CONCENTRATION IN BLOOD AND SERUM FROM "NORMALS" AND EXPOSED WORKERS

		Country	n	Mean	Median	Range	Units	Method	Reference
Blood	"Normals"	Sweden	6	0.5		0.2-0.8	µg/100 g	Neutron Activation	Brune et al., 1961
		U.S.A.	153	0.85	0.70	0.34-5.4	"	Spectrographic after dithizone extraction	Imbus et al., 1963
		U.S.A.	243	<0.5	<0.5	<0.5-14.2	µg/100 ml	Atomic abs. after dithizone extract	Kubota, Lazar and Losee, 1968
		W. Germany	18	0.35			"	Atomic abs. after MIBK-APCD extract	Lehnert (personal communication)
		Sweden	150	<0.2	<0.2		"	Spectrographic	Piscator (unpublished data)
	Exposed workers	Sweden (presently exposed)	22	2.7		0.4-5.8	"	"	"-
		Sweden (not exposed for 10-20 years)	35	0.86		0.3-2.2	"	"	"-
		W. Germany (presently exposed)	22	4.1			"	Atomic abs. after MIBK-APCD extract	Lehnert (personal communication)
Serum	"Normals"	W. Germany	15	0.33		0.12-0.90	"	"-	Lehnert, Schaller and Haas, 1968
		U.S.A.	27	1.2			"	Atomic abs.	Morgan, 1970
		W. Germany	18	0.23			"	Atomic abs. after MIBK-APCD extract	Lehnert (personal communication)
	Exposed workers	W. Germany (presently exposed)	17	0.19		0-0.90	"	"-	Lehnert et al., 1969
		W. Germany (presently exposed)	22	1.37			"	"-	Lehnert (personal communication)

Table 4:4 URINARY EXCRETION OF CADMIUM IN "NORMAL" SUBJECTS

Country	n	Mean	Range	Unit	Method	Reference
U.S.A.	154	1.59	0.5-10.8	µg/l	Spectrographic after dithizone extraction	Imbus et al., 1963
Japan	30	3.1	0-15.9	µg/l	Dithizone	Suzuki, Suzuki and Ashizawa, 1965
W. Germany	14	1.0	-	µg/l	"	Mappes, 1969
W. Germany	10	0.98	0.34-1.57	µg/24 hrs	Atomic abs. after MIBK-APCD extraction	Lehnert, Schaller and Haas, 1968
W. Germany	169	1.25	0-5	µg/g creatinine	"	Szadkowski, Schaller and Lehnert, 1969
Sweden	10	0.39	0.19-0.77	µg/24 hrs	"	Linnman and Lind (unpublished data)

Table 4:5 URINARY EXCRETION OF CADMIUM IN EXPOSED WORKERS

Country	n	Range	Unit	Type of exposure	Method	Reference
France	2	530-1120	µg/24 hrs	CdO dust	Nephelometric	Truhaut and Boudene, 1954
England	12	12- 487	µg/l	CdO dust	Dithizone	Smith, Kench and Lane, 1955
"	10	9- 36[x]	µg/l	CdO dust	"	Smith and Kench, 1957
"	26	14- 428	µg/l	CdO dust	"	Smith and Kench, 1957
"	27	16- 425	µg/l	CdO fume	"	Smith and Kench, 1957
Japan	34	0- 159	µg/l	Cd stearate	"	Suzuki, Suzuki and Ashizawa, 1965
"	13	3- 140	µg/l	CdO fume	"	Tsuchiya, 1967
England	56	0- 168	µg/l	CdO dust	"	Adams, Harrison and Scott, 1969
"	9	6- 74[xx]	µg/l	CdO dust	"	Adams, Harrison and Scott, 1969
W. Germany	18	0.8-6.2	µg/g creatinine	CdO fume CdS	Atomic abs. after MIBK-APCD extraction	Lehnert et al., 1969

[x] Workers in alkaline accumulator factory not directly exposed to cadmium

[xx] Workers with proteinuria without present exposure.

Table 4:6 "NORMAL" CONCENTRATIONS OF CADMIUM IN HAIR

Country	Sex	n	μg/g Mean ± S.D.	Median	Range	Method	Reference
U.S.A	Male	82	2.77 ± 4.37			Atomic abs. Hair not treated with detergent solution	Schroeder and Nason, 1969
	Female	47	1.77 ± 1.64			"	"
U.S.A.	Male children[x]	45	3.5 ± 4.94	2.1		Atomic abs. Hair pretreated with EDTA	Hammer et al., 1970
		25	2.0 ± 1.54	1.6			
		37	1.3 ± 0.99	1.0			
		21	1.3 ± 1.30	0.9			
		37	0.9 ± 0.8	0.8			
Sweden	Male	7	0.44 ± 0.14	0.43	0.24-0.60	Atomic abs. Hair pretreated with detergent	Nishiyama (personal communication)
	Female	8	0.87 ± 0.26	0.92	0.41-1.27	"	"
Yugoslavia Rural area	Male	17	0.54 ± 0.27	0.45	0.20-1.48	"	

[x] 10 years of age from 5 areas with differing degrees of cadmium contamination

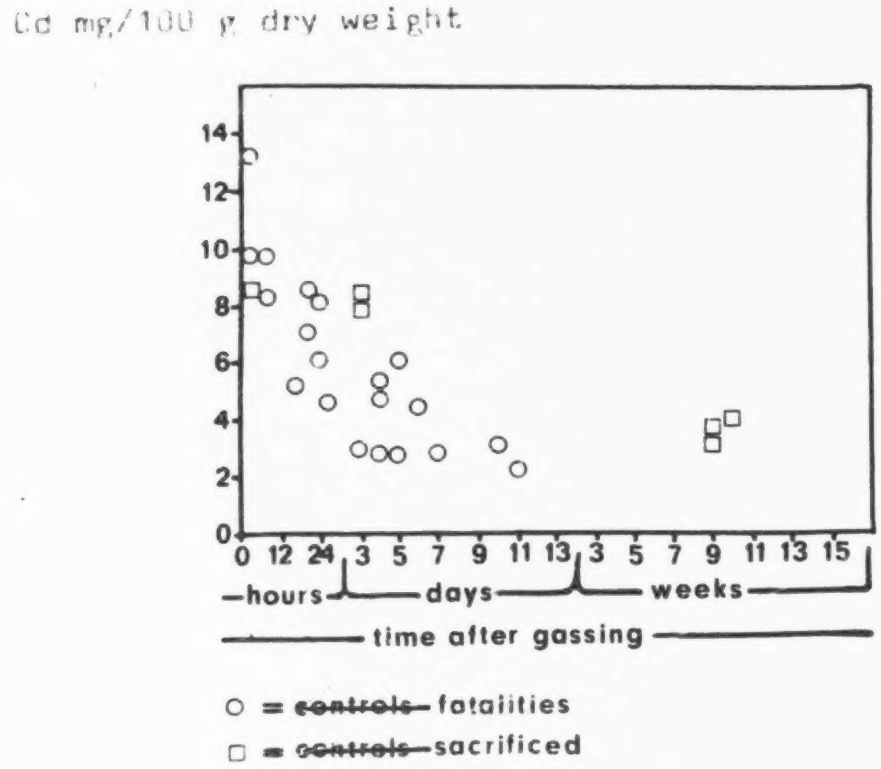


Figure 4:1 Concentrations of Cadmium in Lungs of Dogs at Intervals Following Exposure to Cadmium Chloride Aerosols (modified from a figure by Harrison et al., 1947).

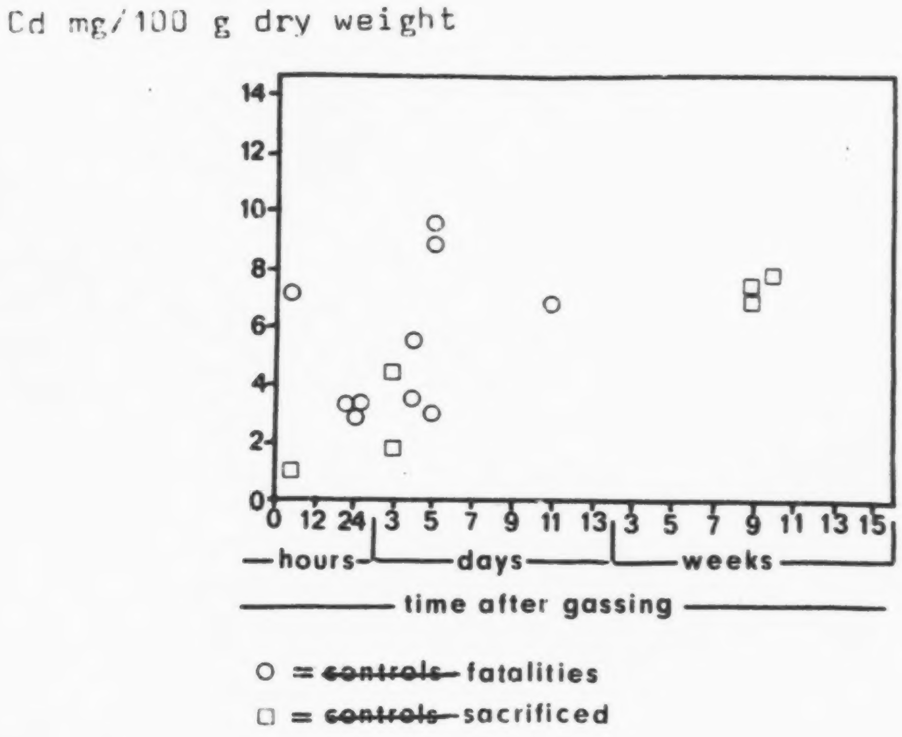


Figure 4:2 Concentrations of Cadmium in Kidneys of Dogs at Intervals Following Exposure to Cadmium Chloride Aerosols (modified from a figure by Harrison et al., 1947).

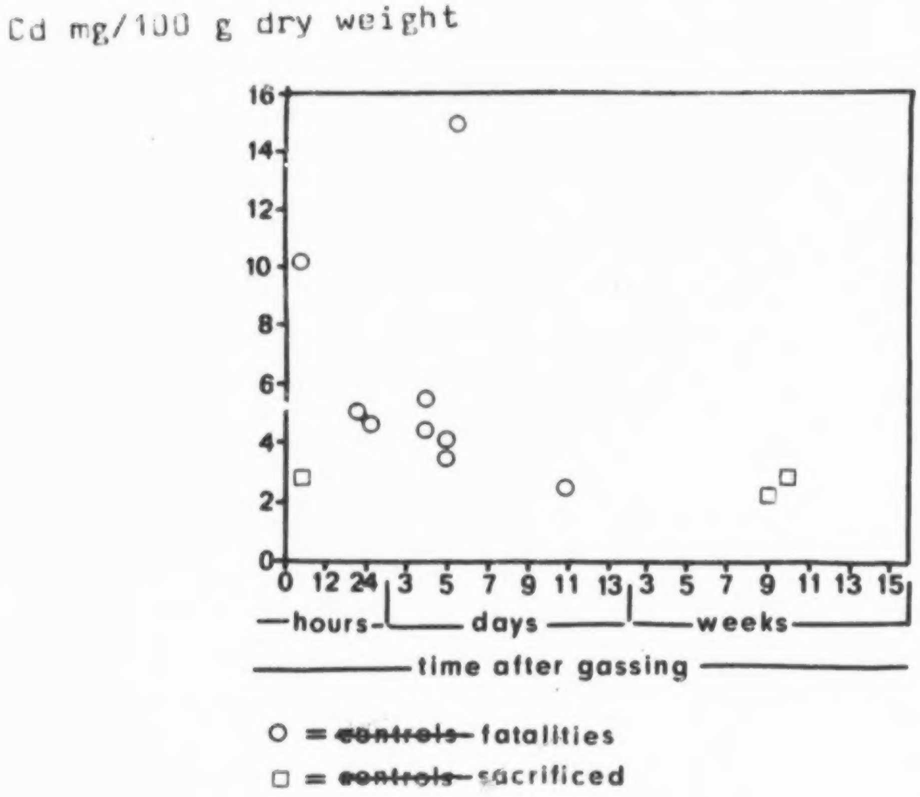


Figure 4:3 Concentrations of Cadmium in Liver of Dogs at Intervals Following Exposure to Cadmium Chloride Aerosols (modified from a figure by Harrison et al., 1947).

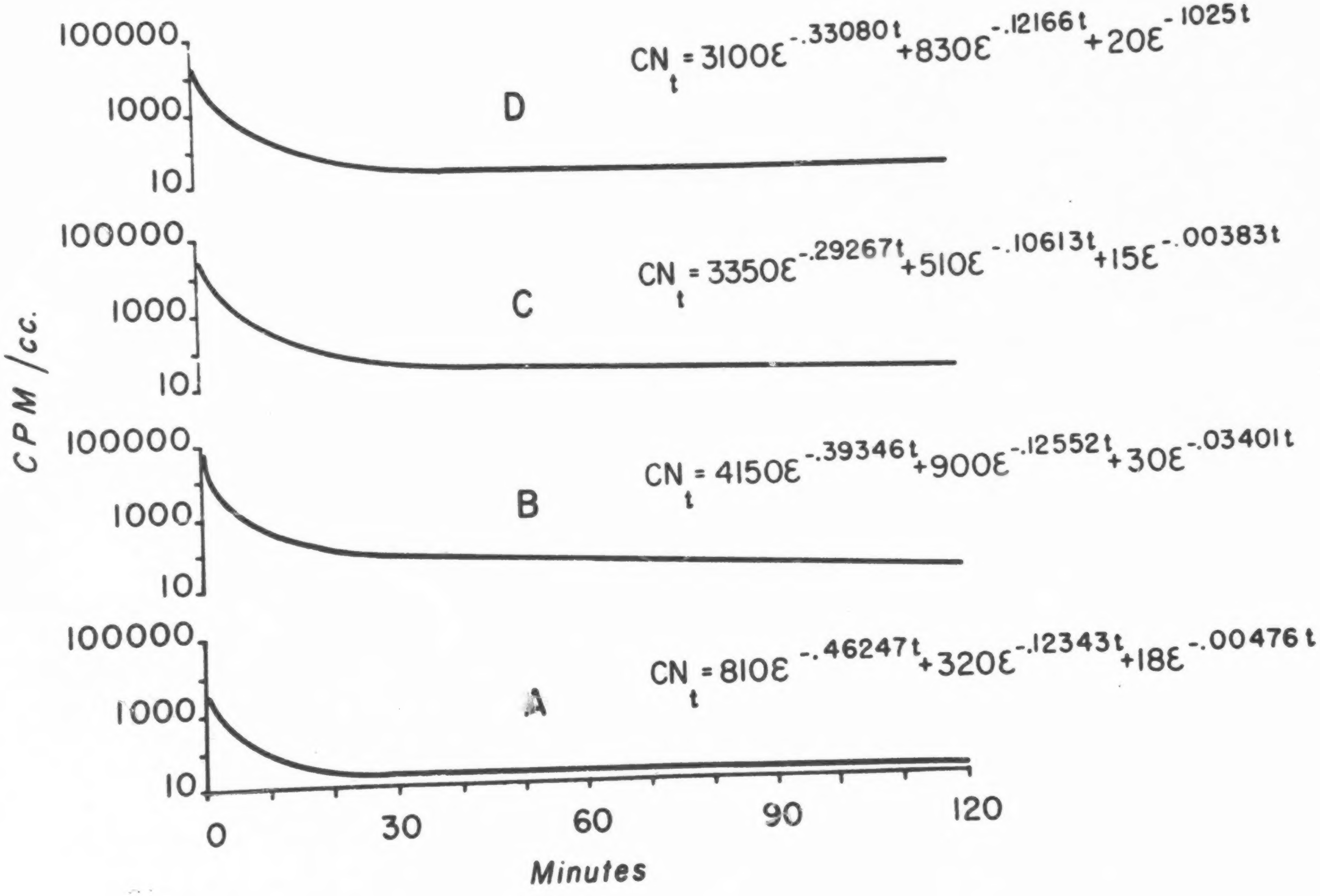
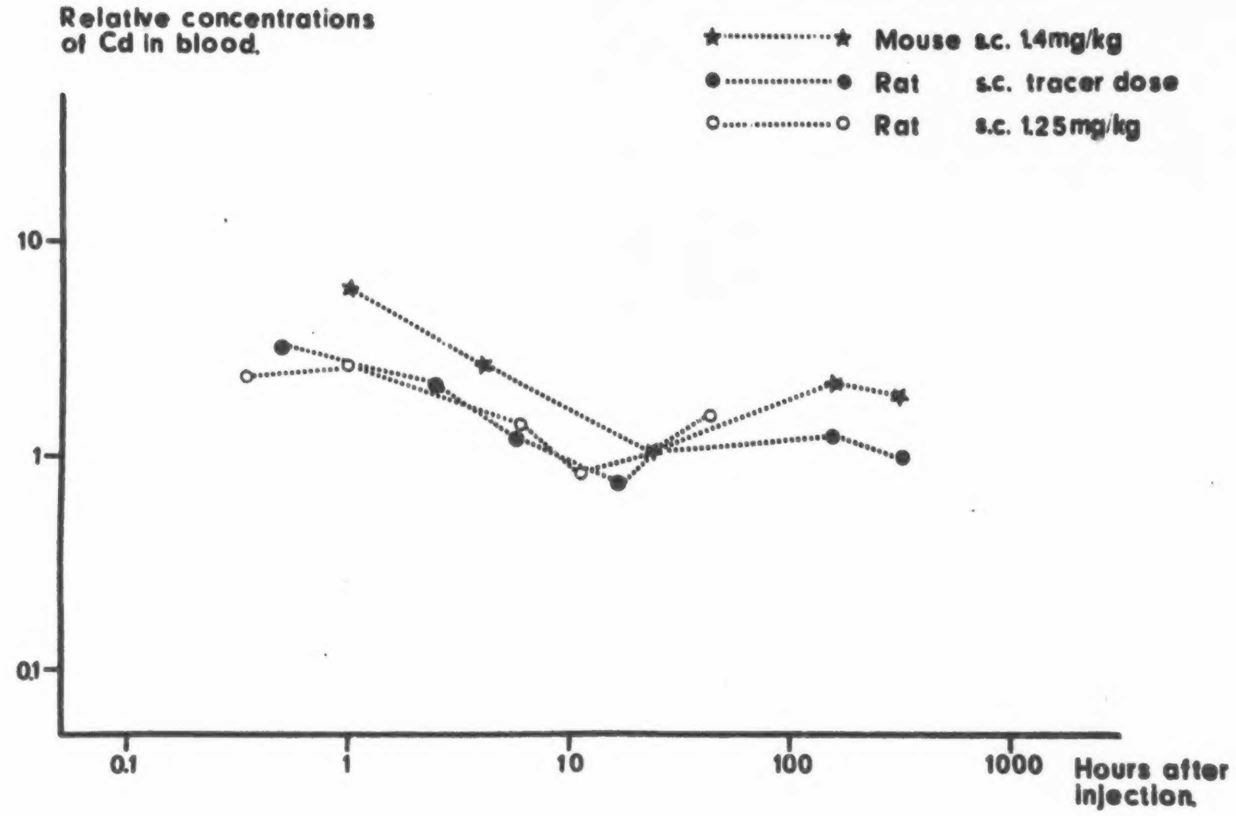
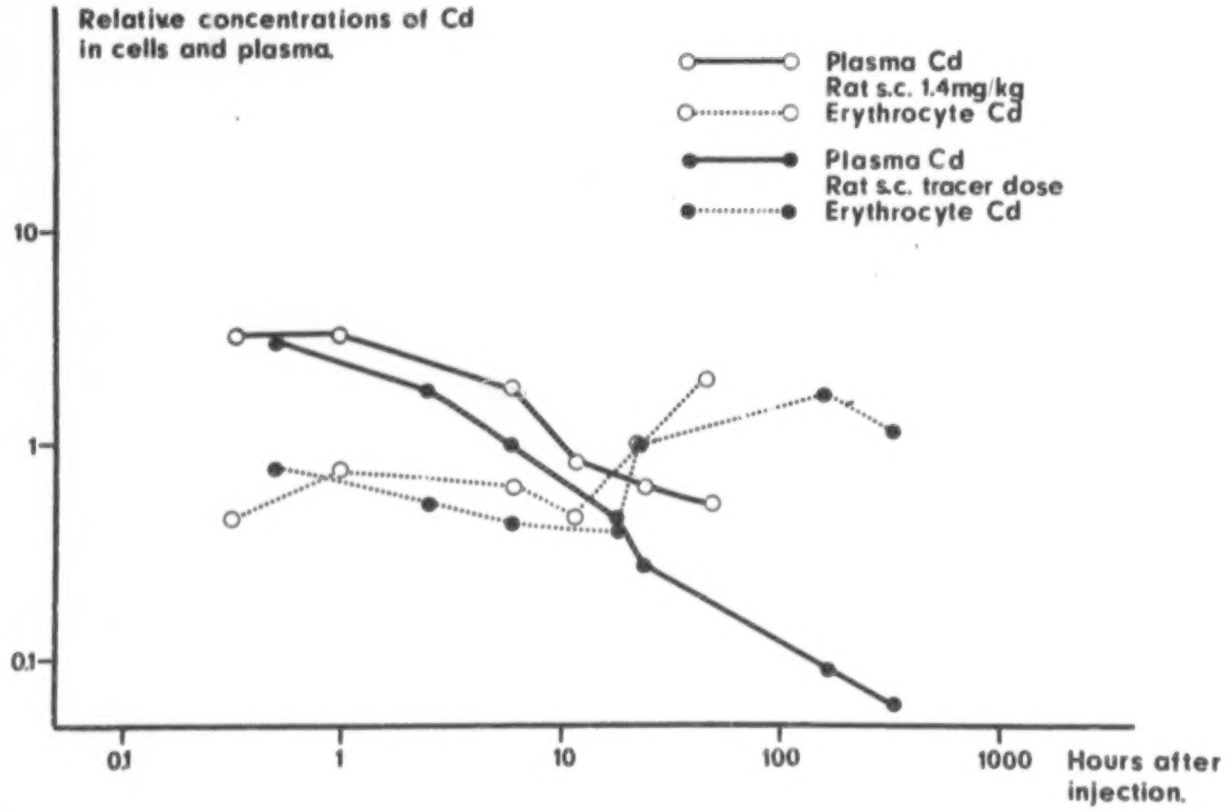


Figure 4:4 Disappearance of Cadmium from Plasma after an Intravenous Injection of ^{115}Cd-nitrate$_2$ (from Walsh and Burch, 1959).



In each report the concentration in blood after 24 hours has been set at 1.0 and concentrations at other times are expressed in relation to the concentrations at 24 hours. For calculation of whole blood values from cell and plasma concentrations it has been assumed that the cells constitute about 45 percent of the whole blood.

Figure 4:5 Concentrations of Cadmium in Blood Related to Time after Subcutaneous Injections of Cadmium in Rats and Mice (from data by Eybl, Sýkora and Mertl, 1966a, Gunn, Gould and Anderson, 1968a, and Lucis, Lynk and Lucis, 1969).



In each report the concentration in the cells after 24 hours has been set at 1.0 and the concentrations in cells and plasma are expressed in relation to the concentration in cells at 24 hours.

Figure 4:6 Concentration of Cadmium in Cells and Plasma Related to Time after Subcutaneous Injections in Rats (from data by Eybl, Sýkora and Mertl, 1966a and Lucis, Lynk and Lucis, 1969).

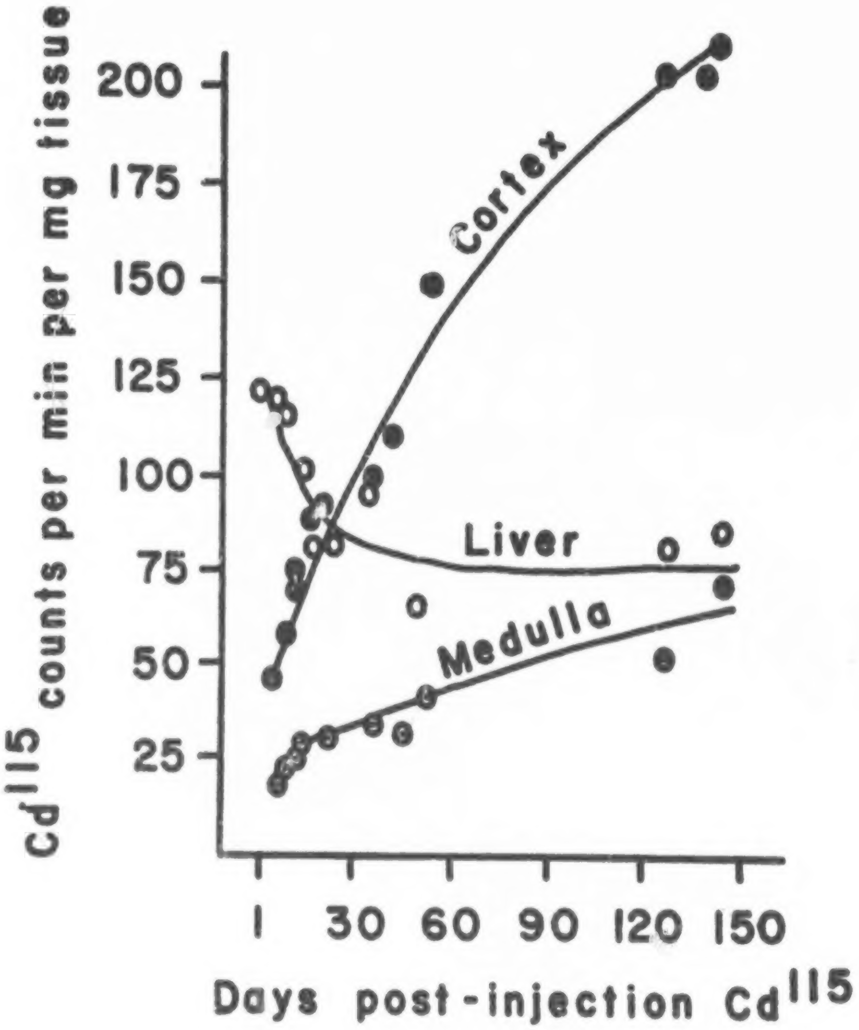


Figure 4:7 Accumulation of Cadmium in Kidney and Liver of Rats after Intracardiac Injection (from Gunn and Gould, 1957).

NOT REPRODUCIBLE

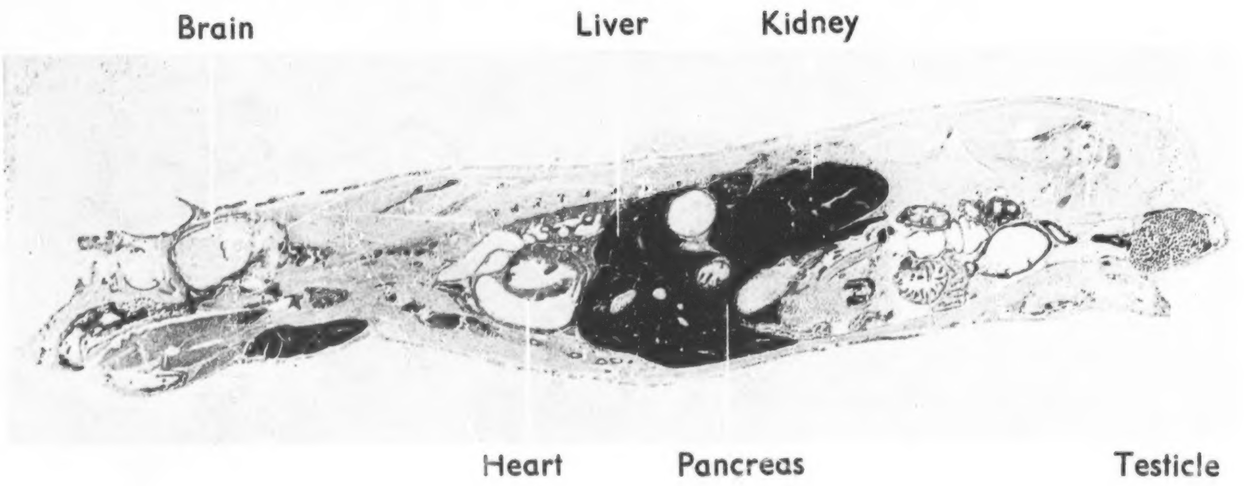
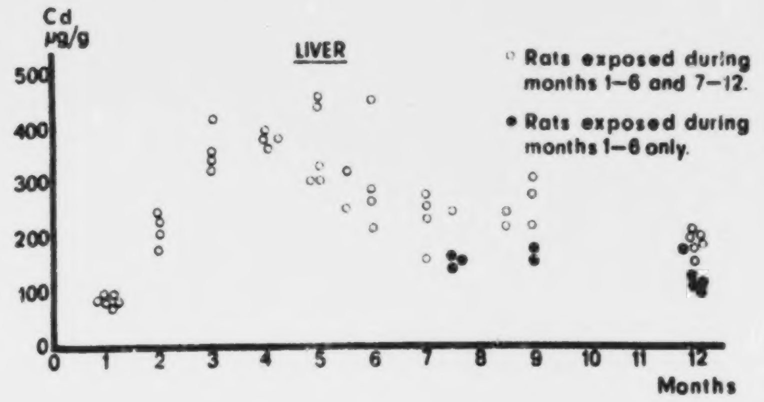
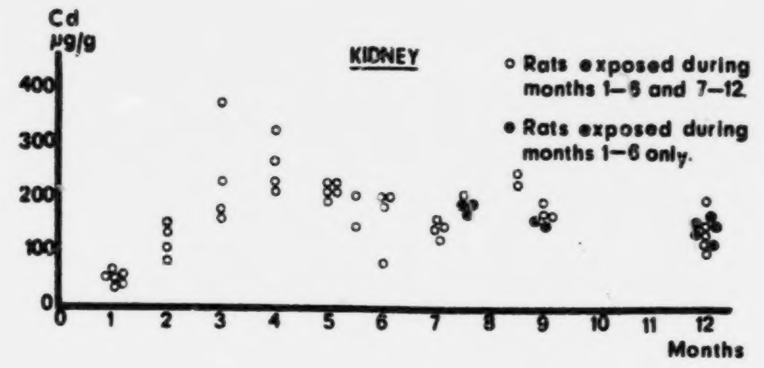

Brain
Liver
Kidney
Heart
Pancreas
Testicle

Fig 4:8 Autoradiographic distribution of ^{109} Cd in a Mouse 112 days after a Single Intravenous Injection (from Nordberg, unpublished data).



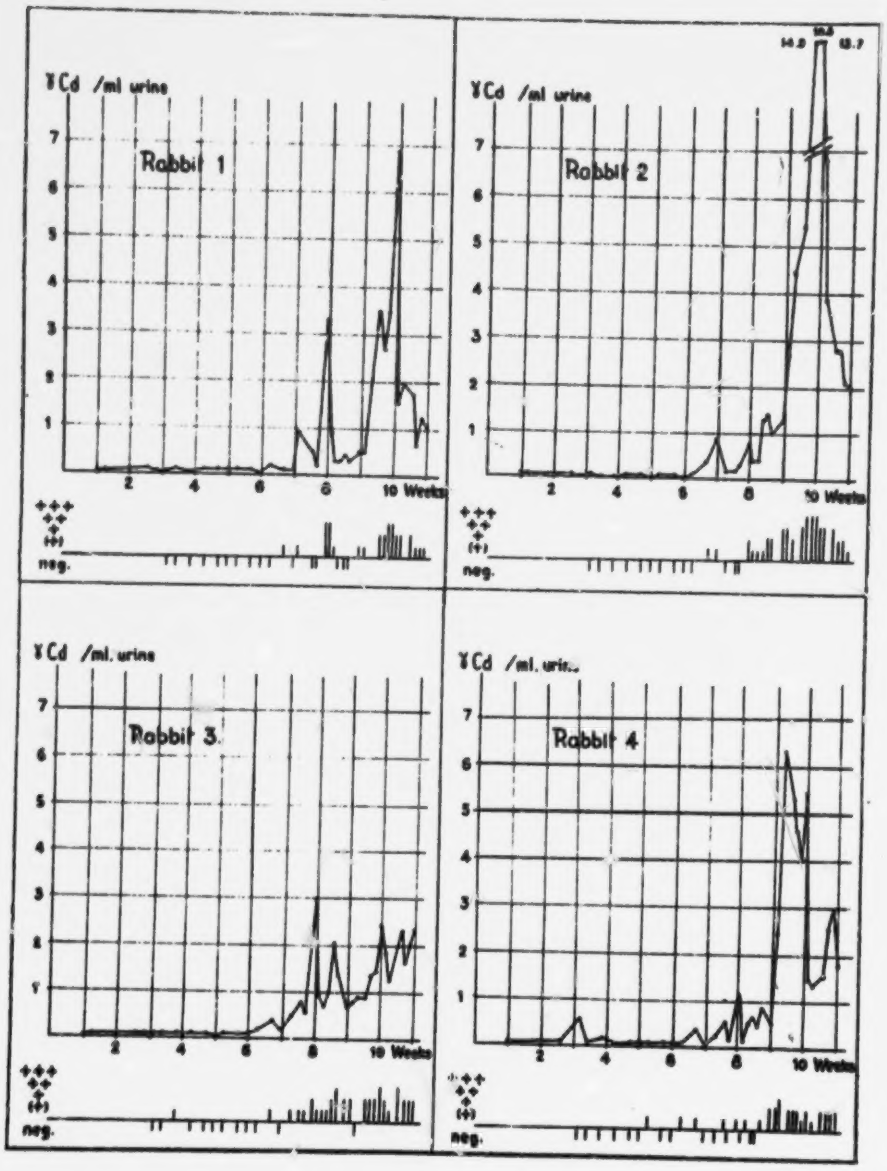
Intraperitoneal injections 0.75 mg Cd/kg three times a week, months 1-5 or 6; 0.25 mg Cd/kg three times a week, months 7-12.

Figure 4:9 Cadmium Concentrations in Liver of Rats Exposed to Cadmium Chloride (modified from a figure by Bonnell, Ross and King, 1960)



Intraperitoneal injections: 0.75 mg Cd/kg, three times a week, months 1-5, or 6; 0.25 mg Cd/kg three times a week, months 7-12.

Figure 4:10 Cadmium Concentrations in Kidney of Rats Exposed to Cadmium Chloride (modified from a figure by Bonnell, Ross and King, 1960).



(+) = proteinuria demonstrated only with trichloracetic acid

+ - +++ = proteinuria demonstrated also with nitric acid

Figure 4:11 Cadmium Concentrations and Occurrence of Protein in Urine of Cadmium Exposed Rabbits (from Friberg, 1952).

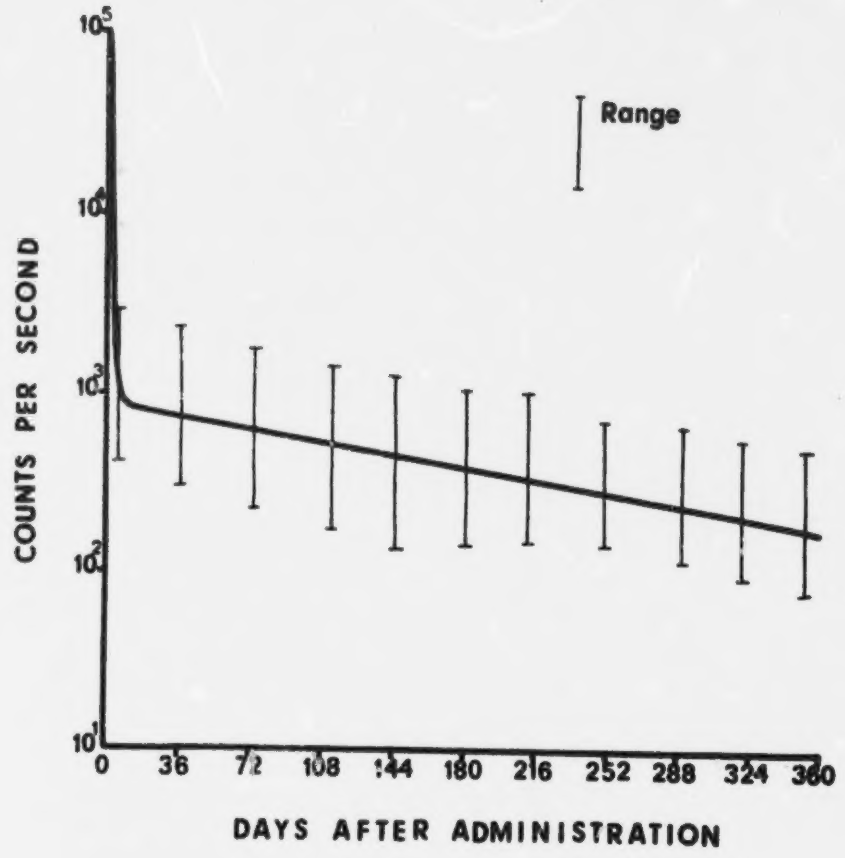


Figure 4:12 Whole-Body Retention of Orally Administered ^{109}Cd in 8 Mice (modified from a figure by Richmond, Findlay and London, 1966).

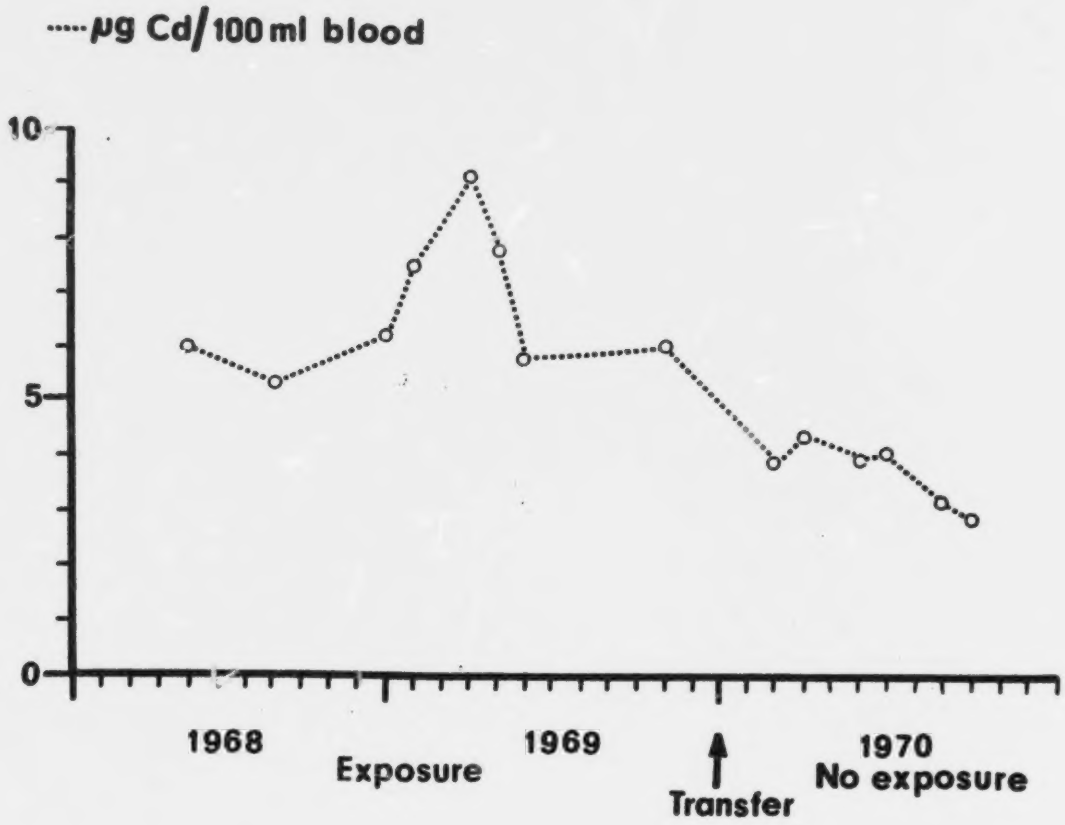


Figure 4:13 Cadmium Concentrations in Blood from a Worker during and after Exposure to Cadmium Oxide Fumes (Spectrographic Method) (from Rogenfeldt, personal communication).

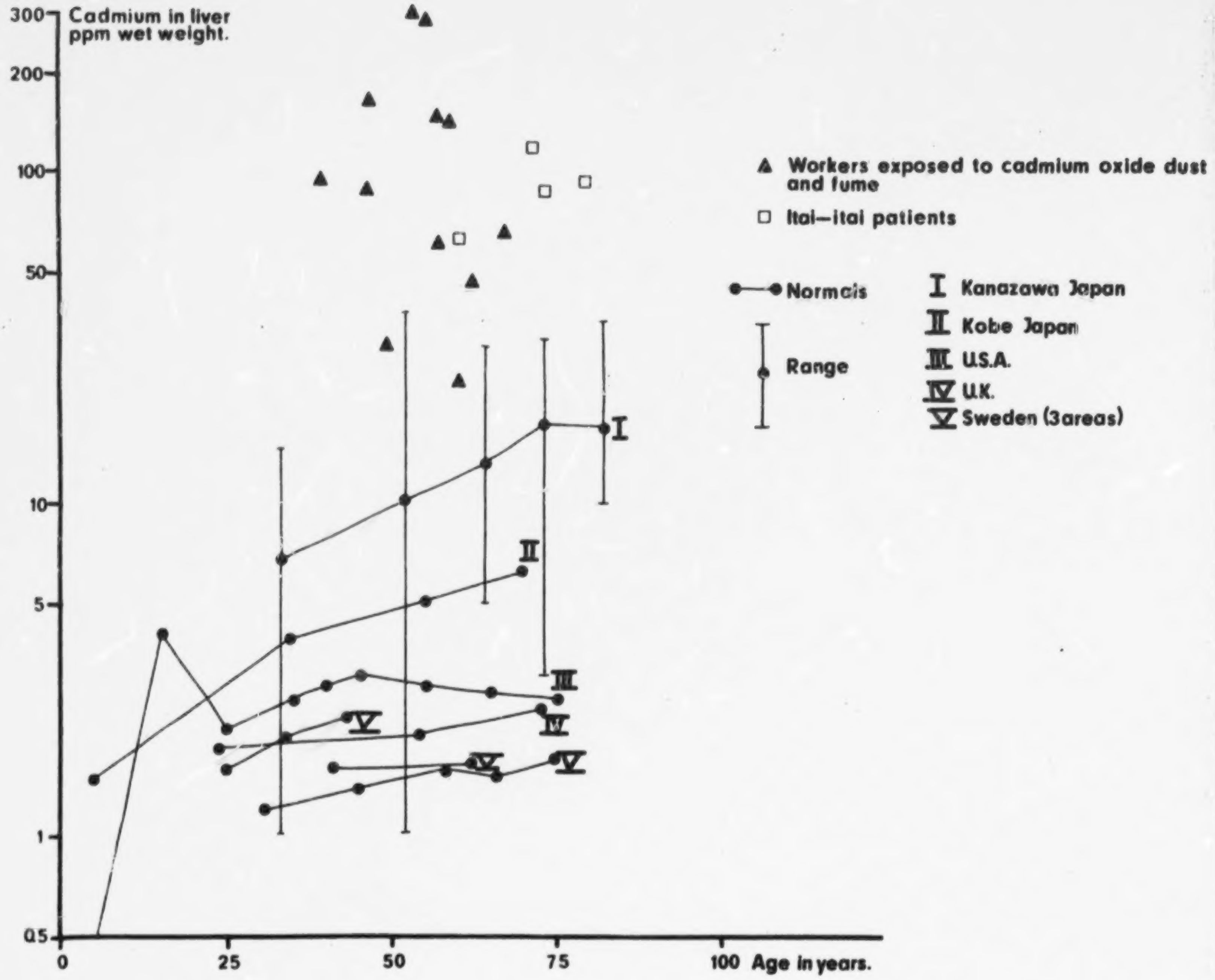


Figure 4:14 Cadmium Concentrations in Liver from Norman Human Beings in Different Age Groups (mean values), Exposed Workers (single values) and Itai-itai Patients (single values) (data on normal human beings from Kanazawa, Japan - Ishizaki, Fukushima and Sakamoto, 1970b,
Kobe, Japan - Kitamura, Sumino and Kamatani, 1970
U.S.A. - Schroeder and Balassa, 1961, Schroeder et. al., 1967
United Kingdom - Curry and Knott, 1970
Sweden - Piscator, unpublished data

data on exposed workers, see figure 4:15
data on Itai-itai patients - Ishizaki, Fukushima and Sakamoto, 1970b).

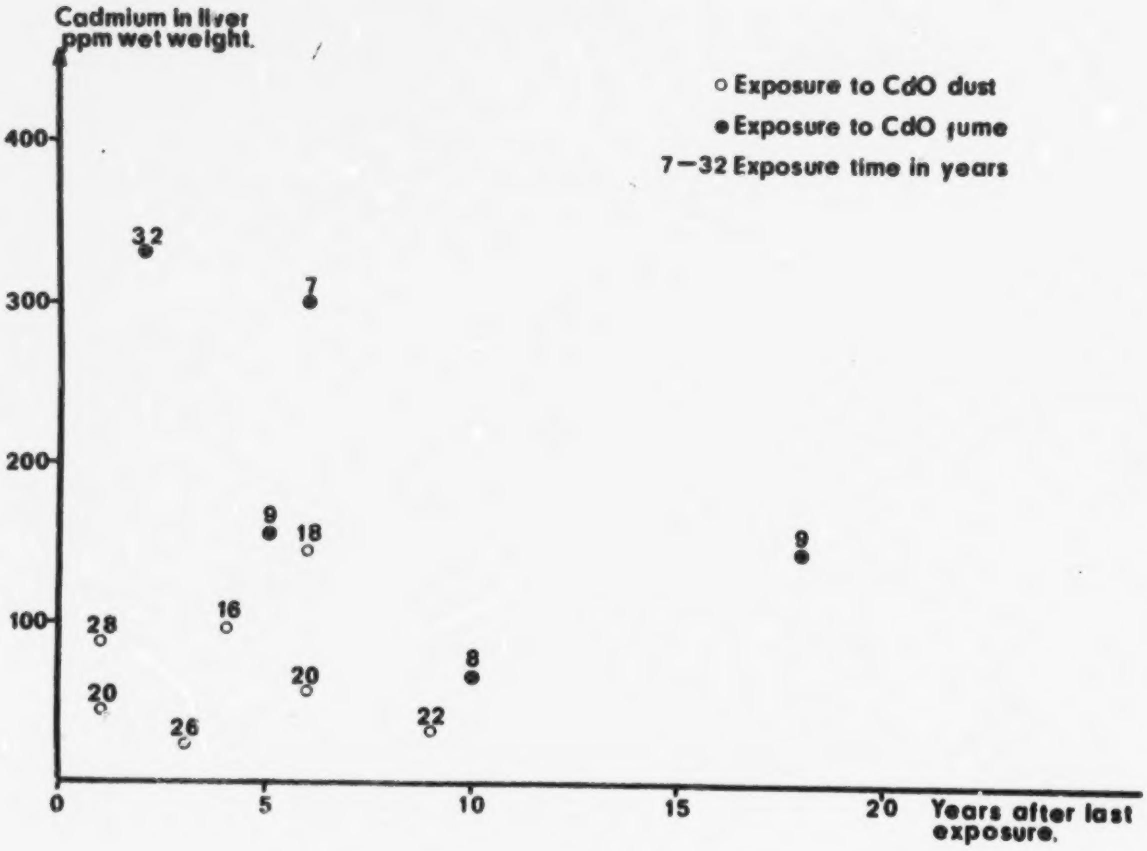


Figure 4:15 Cadmium Concentrations in Livers of Exposed Workers in Relation to Time Since Exposure Ceased (from data by Bonnell, 1955, Friberg, 1957, Smith, Smith and McCall, 1960, Kazantzis et al., 1963, and Piscator, unpublished data).

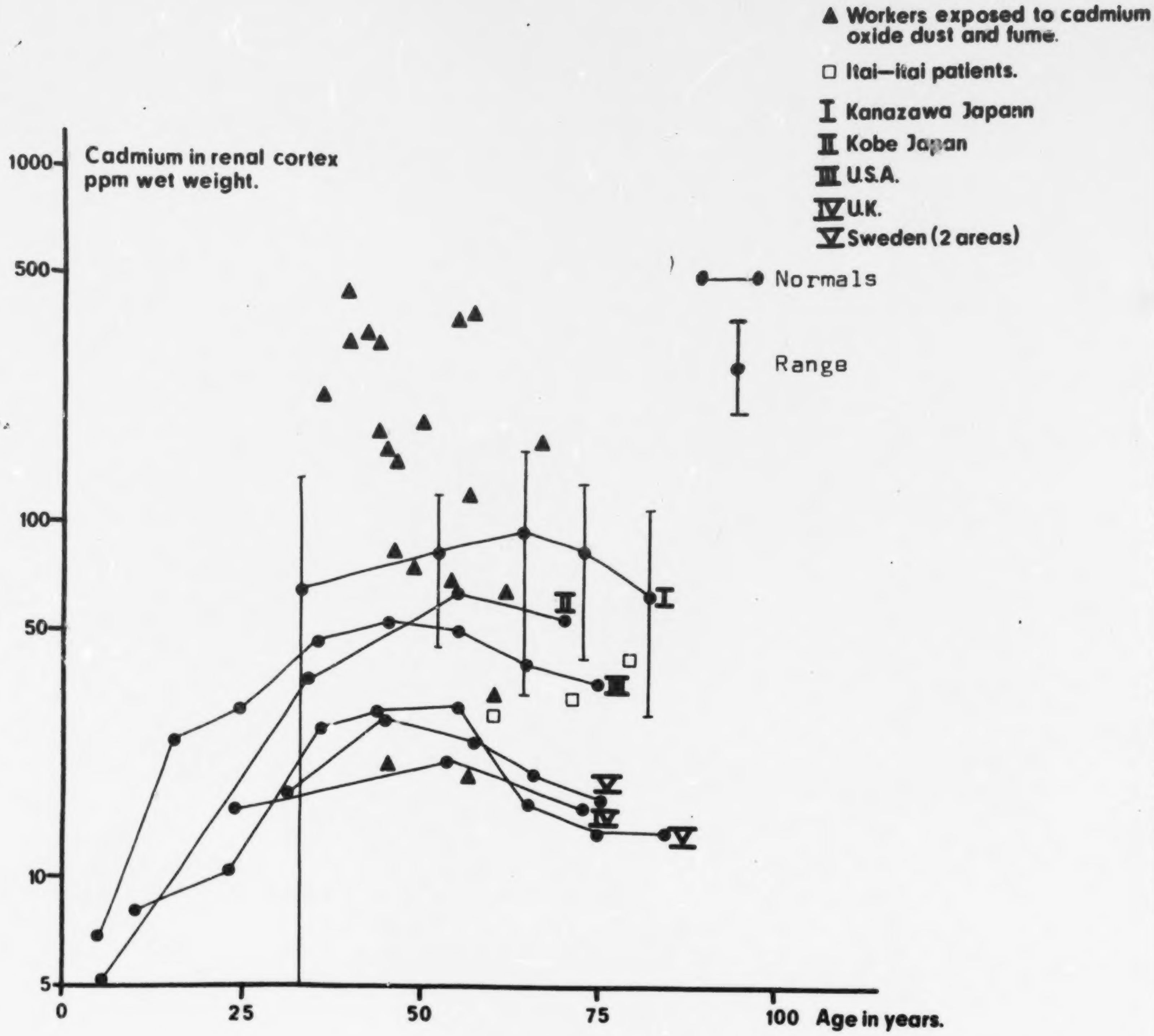


Figure 4:16 Cadmium Concentrations in Renal Cortex from Normal Human Beings in Different Age Groups (mean values), Exposed Workers (single values) and Itai-itai Patients (single values) (data from reports cited in figures 4:14 and 4:15 and from some determinations of renal cadmium in biopsies from cadmium workers, see table 6:1).

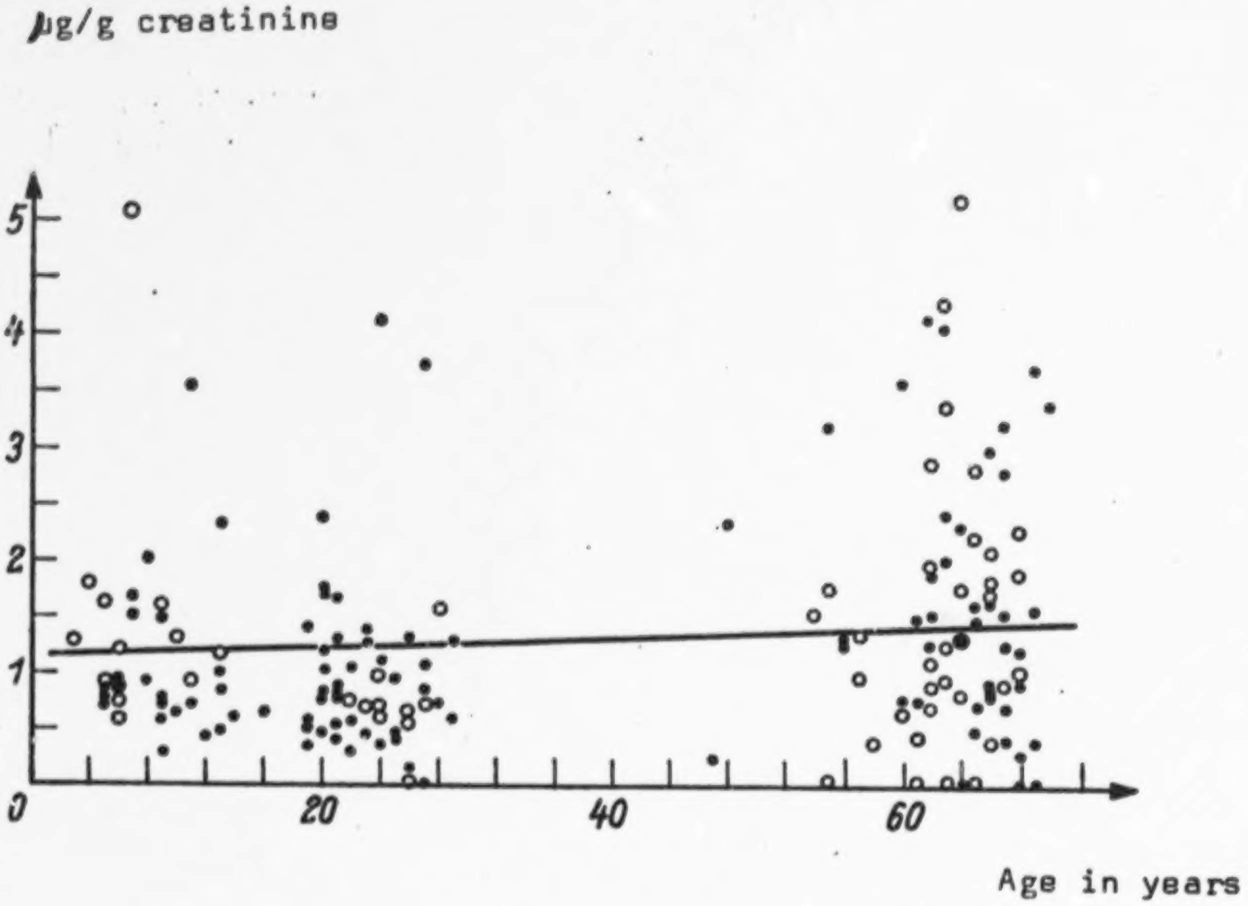


Figure 4:17 Cadmium Excretion in Relation to Age (from Szadkowski, Schaller and Lehnert, 1969).

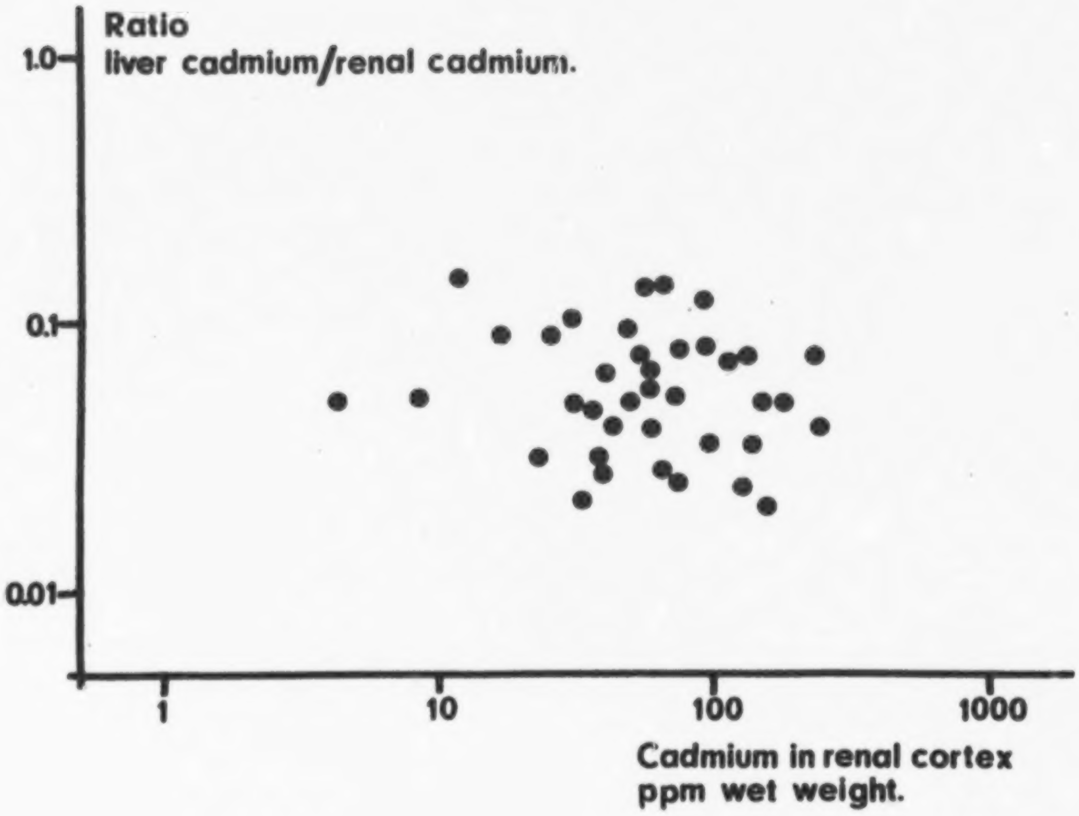


Figure 4:18 Ratio between Liver and Renal Cortex Concentrations of Cadmium in Relation to Cadmium Concentrations in Renal Cortex in Horse (from Piscator, unpublished data).

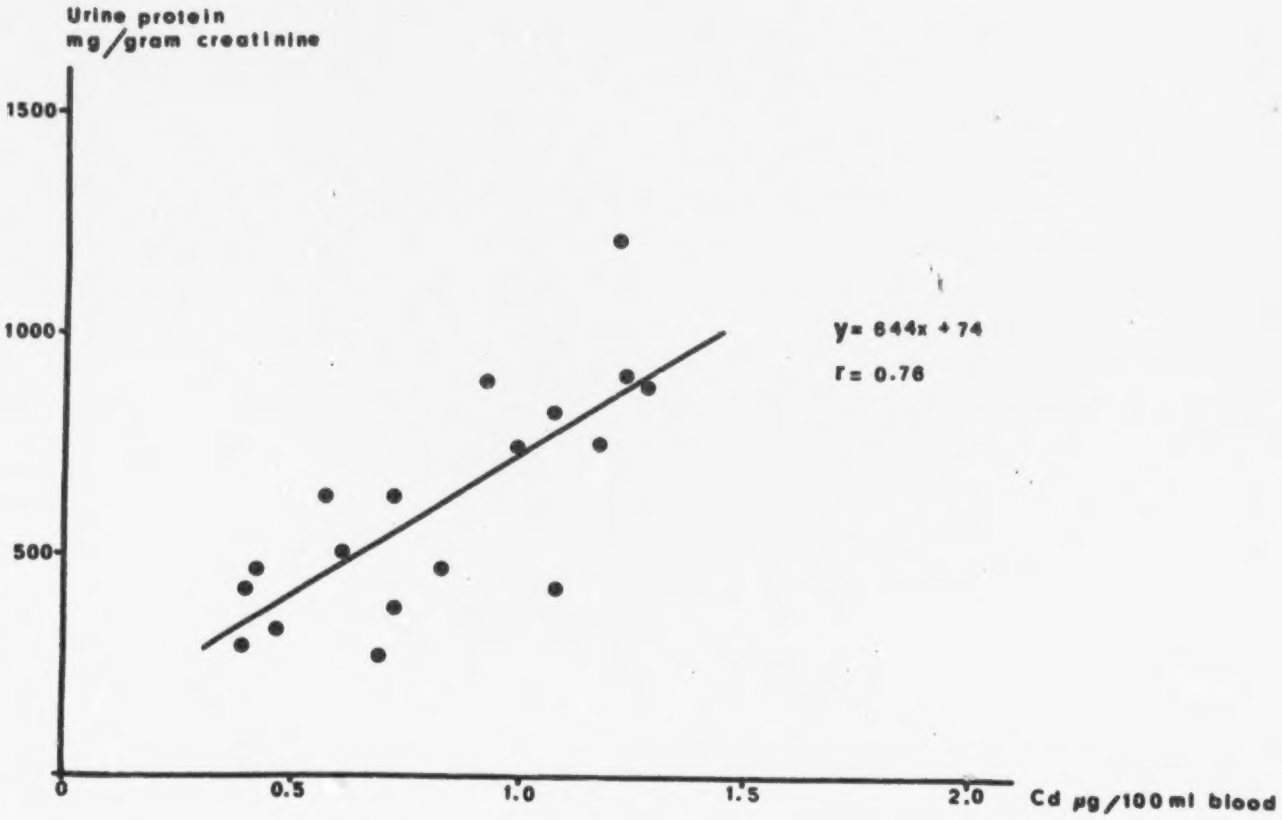


Figure 4:19 Urinary Protein Excretion in Relation to Blood Concentrations of Cadmium in Workers with Earlier Exposure to Cadmium but not Exposed during the Last 20 Years (from Piscator, unpublished data).

CHAPTER 5

RESPIRATORY EFFECTS AND DOSE-RESPONSE RELATIONSHIPS

Much evidence has been collected and entered in the literature showing the severe and extensive respiratory effects in human beings exposed in industries and in animals exposed in laboratories to various cadmium compounds. These symptoms can be noted in cases of acute exposure to high concentrations as well as in cases of chronic exposure to low concentrations of cadmium. In this review special attention will be given to the effects of chronic exposure. As the acute effects serve to show the potential hazards of cadmium, a brief review is given also of the nature of such effects as well as the concentration ranges associated with them.

5.1 ACUTE EFFECTS AND DOSE-RESPONSE RELATIONSHIPS

In 1932, Prodan reported acute effects in animals which had inhaled cadmium compounds. Since that time, several reports verifying the deleterious effects on the lungs of both animals and human beings have been published. Some data have been recorded regarding dose-response relationships for different species.

Paterson, 1947, described in detail the pathology in rats acutely poisoned with cadmium through inhalation of finely dispersed cadmium oxide or cadmium chloride aerosols. The findings, similar for both exposure types, were confined to the lungs. The three clearly demarcated stages were 1) acute pulmonary oedema, developing within twenty-four hours of exposure, 2) proliferative interstitial pneumonitis, observed from the third to tenth days after exposure, and 3) permanent lung damage in the form of perivascular and peribronchial fibrosis. Similar findings, including long-term effects of an emphysematous nature, have been reported by Thurlbeck and Foley, 1963.

The first two of the demarcated stages described in animal studies could be confirmed clinically or at autopsy on human beings exposed during, for example, welding or cutting materials containing cadmium (Paterson, 1947, Huck, 1947, Reinl, 1961, Lamy et al., 1963, Kleinfeld, 1965, Blejer, Caplan and Alcocer, 1966, Beton et al., 1966, and Townshend, 1968).

The question of whether a nonfatal acute exposure can produce long-term effects in human beings does not seem to have been properly studied on a large number of cases. Townshend, 1968, reported one case of pulmonary oedema caused by acute cadmium poisoning which was observed over a period of 4 years. Tests showed a gradual improvement of the lung function during the first 6 months. Four years later the CO diffusing capacity was normal but the forced vital capacity was less than 80 percent of the predicted value. Similar studies on larger groups exposed acutely to cadmium are greatly needed.

Human data regarding dose-response relationships are quite scarce. From animal experiments evidence is fairly well documented concerning the acute mortality rate after short-term exposure to cadmium oxide fumes, the type of exposure occurring in connection with most of the reported human cases.

Earlier mentioned studies by Harrison et al., 1947 (4.1.1.2) showed an LD_{90} in dogs of 320 mg/m^3 over a 30-minute exposure to a cadmium chloride aerosol (9600 min · mg/m^3). Barrett, Irwin and Semmons, 1947, gave data from exposure of a substantial number of rats, mice, guinea pigs, rabbits, dogs and monkeys to cadmium oxide fumes. The exposure periods lasted from 10 to 30 minutes. The LD_{50} (cumulative mortality up to 7-28 days) varied between 500 and 15,000 min · mg/m^3 depending on animal species (table 5:1).

Based on the amount of cadmium found in the lungs and the lung ventilation for the different species, the authors calculated the retention of cadmium, to about 11 percent. This did not differ markedly among the species. They also calculated the dose for two fatal human cases described by Bulmer, Rothwell and Frankish, 1938, and Paterson, 1947, to 2500 min · mg/m^3. Starting points were observed values of cadmium in the lungs corresponding to 1.8 and 1.7 mg cadmium oxide per 100 g of dry tissue, respectively, and an assumption that the percentage of retention of cadmium oxide fumes for man was the same as for animals.

An independent check on this calculated dose was made by Barrett and Card, 1947. They tried to reproduce the actual exposure conditions.and measured the cadmium concentrations formed. They concluded that a lethal concentration of thermally generated cadmium oxide fume for man doing light work is not over 2900 min · mg/m^3 and would possibly be as little as half of this value for arc produced fume. Beton et al., 1966, applied to a fatal case of cadmium poisoning the type of calculations used by Barrett, Irwin and Semmons, 1947. With an observed concentration of cadmium oxide in the lungs of 0.25 mg/100 g of wet weight, they reached the conclusion that the concentration times exposure time should have been around 2600 min · mg/m^3. The exposure time in this case was five hours and the authors calculated an average lethal concentration for this exposure time to be around 8.6 mg/m^3 for cadmium oxide fumes. For 8 hours exposure, a lethal concentration would then be around 5 mg/m^3.

The authors pointed out the uncertainty in regard to some of the assumptions necessary for the calculations. There could be no doubt that such uncertainties existed. Furthermore, the used "retention value" of 11 percent was with all probability considerably lower than the "retention value" immediately after the exposure. As a value of 11 percent was used in both the animal studies and in the calculations for human beings, any error tends to be cancelled out, however. There are reasons to accept a figure of about 5 mg cadmium oxide $fumes/m^3$ over an eight hour period as a probable lethal concentration for man.

By no means must 5 mg/m^3 be the lowest which can give rise to fatal poisoning. It is known from animal experiments (Paterson, 1947) that exposure to concentrations of only about one-fourth the LD_{50} can give rise to acute symptoms and to a significant degree of permanent lung damage. Even without applying a safety factor when extrapolating from animal data, there is thus reason to regard a concentration of around 1 mg/m^3 over an eight hour period as immediately dangerous, for human beings with reference to cadmium oxide fumes.

For cadmium dust, the data necessary to perform similar estimations are not available. Friberg, 1950, however, determined LD_{50} for 7 groups of 8 rabbits for a cadmium-iron oxide dust (proportion Cd to Fe: 3:1, observation period: 14 days). On an average, about 95 percent of the particles were smaller than 5 microns and about 55 percent smaller than 1 micron (coniometer method). The rabbits were exposed for 4 hours and LD_{50} calculated as the product of concentration and exposure time was about 11,000 $min \cdot mg/m^3$.

Taking only the cadmium oxide part of the dust into consideration, the LD_{50} for cadmium oxide dust would be about 8000 min · mg/m^3 , i.e., about three to four times the values for cadmium oxide fumes (for rabbits: 2500). For an 8 hour exposure, this gives a concentration of about 17 mg/m^3 of cadmium oxide dust for rabbits.

5.2 CHRONIC EFFECTS AND DOSE-RESPONSE RELATIONSHIPS

5.2.1 In human beings

5.2.1.1 Industrial exposure

There are in the earlier literature, Stephens, 1920, scanty data suggesting a chronic cadmium poisoning in human beings. With the knowledge available today, it can further be said that some early reports of plumbism might instead have been cadmium poisoning. When Seiffert, 1897, described 65 cases of chronic lead poisoning among workers in a zinc smelter, he thus reported emphysema among 83 percent and proteinuria among 82 percent of these workers. No doubt there must have been a considerable exposure also to cadmium and the symptoms described fit chronic cadmium poisoning.

5.2.1.1.1 Respiratory effects reported - exposure to cadmium dust

The first reports of lung emphysema in chronic cadmium poisoning were given by Friberg, 1948a and b, and in more detail by Friberg, 1950, in studies among male workers exposed to cadmium oxide dust in an alkaline accumulator factory in Sweden. Complaints of shortness of breath were common. An impaired lung function was demonstrated as an increased residual capacity in relation to total lung capacity. It was shown that the impairment of lung function was closely associated with a poor physical working capacity evaluated with a standardized working test on a bicycle-ergometer. (figure 5:1).

The Swedish reports referred to above covered 43 male workers with an average time of employment of 20 years (range: 9-34 years). Another group of 15 workers, similarly exposed, among whom the lung function was normal, had been employed for only 1-4 years. All workers had been exposed to a mixture of cadmium iron oxide dust and nickel graphite oxide dust. Quantitative data concerning the exposure were incomplete, as air analyses were made only upon one occasion and only at five places (over about 30 minutes on each place) in the working rooms. The amount of cadmium in the air varied between 3 to 15 mg/m^3. Time weighted 8-hour averages values were not calculated but were probably lower. Respiratory masks were provided but stated to be used rarely.

The Swedish findings were confirmed at a similar German factory by Baader, 1951 and 1952. Out of 8 workers exposed 8-19 years, 6 had emphysema as judged by clinical and X-ray examinations. Complaints of coughing and shortness of breath were common. No quantitative analysis about the exposure was given.

Several other reports of lung damage have since been made. Vorobjeva, 1957, reported "diffuse pulmonary sclerosis" among female workers in the production of alkaline accumulators. From the same type of factory in Britain, Potts, 1965, reported bronchitis in 6 men, and associated emphysema in 4. Diagnostical methods were not discussed. In a later report from the same factory, Adams, Harrison and Scott, 1969, found a decrease in forced expiratory volume (FEV$_1$) in male workers.(figure 5:2). Twenty-seven male workers were covered. Their exposure times were not obvious from the report, but seem to have varied from 15 to 40 years. Cadmium in air estimations were reported beginning from 1957. Before that time, regular analyses were not carried out. In one working area in the factory, most values varied between 0.5-5 mg Cd/m^3, in a second between 0.1-0.5, and in a third, mostly around 0.1 mg Cd/m^3. It is not possible from the report to evaluate the exposure before 1957. The extent to which respirators were worn was not stated.

Kazantzis et al., 1963, reported emphysema in cadmium pigment workers. Thirteen men had been exposed to a variety of cadmium compounds, of which cadmium sulphide based pigments were by far the most abundant. In addition to cadmium sulphide, the compounds included cadmium seleno-sulphide, cadmium zinc sulphide, cadmium carbonate, cadmium hydroxide and cadmium oxide dust and fume. Out of 6 men engaged in the manufacture of cadmium pigments for 25 years or more, 3 had mild respiratory symptoms and showed slight but definite impairment of ventilatory function with a low FEV_1 percentage (56-61) and a high time constant (1.08 - 1.38 seconds). A fourth man had died at the age of 46 from respiratory insufficiency and right-sided heart failure due to emphysema. It was concluded that the emphysema was caused by exposure to cadmium. Concerning the exposure, the report contains no data on air concentrations of cadmium. The exposure times were as follows: 25 to 31 years for 6 of the workers, 12 to 14 years for 4 of the workers, and 1/2 to 2 years for 3 of them.

5.2.1.1.2 Respiratory effects reported - exposure to cadmium oxide fume

British researchers have published several reports on chronic cadmium poisoning in men exposed to cadmium oxide fumes in casting copper cadmium alloys. Emphysema has been prominent among the symptoms. Lane and Campbell, 1954, thus reported two fatal cases among men making a cadmium copper alloy for less than two years. The general exposure was given as 0.1-0.4 mg Cd/m^3. For very short periods, however, the men had been exposed to high concentrations of cadmium metal fume (actual concentrations not given). Bonnell, 1955, examined 100 exposed men and 104 controls from two factories. The respiratory function was tested by measuring the vital capacity, the maximum ventilatory capacity at controlled rates of breathing, and the expiratory fast vital capacity. Swept fractions at given respiratory rates were calculated. Among the exposed workers 11 were diagnosed as having emphysema. There is no mention of emphysema in the controls. On a group basis significant differences were found between exposed and controls. In factory A the vital capacities and the maximum ventilatory capacities were similar in the two groups, but the mean swept fractions at 30, 50 and 70 respirations per minute were significantly lower in the exposed group. A significant difference was also found between the groups for the mean time constant of the expiratory fast vital capacity curve. In factory B the mean time constant for the expiratory fast vital capacity curve differed significantly between the exposed group and the control group. The other test results were similar in the two groups. The results of these tests are discussed in more detail by Kazantzis, 1956.

Some further studies were made on 37 exposed men from factory B (Buxton, 1955). The men with more than 10 years' exposure showed a significant increase in the mean value of the residual air expressed as a percentage of the total lung volume, (mean: 43.9%, S.D.: 10.3%) compared with a control group (mean: 34.6%, S.D.: 8.3%) and workers exposed less than 10 years (mean: 36.6%, S.D.: 10.9%). The workers in the "cadmium groups" had been exposed from 1 1/2 to 28 years, and those with a recognized emphysema from 7 to 27 years. King, 1955, has made a careful study to evaluate the exposure conditions at the time of Buxton's medical investigations. It is obvious from King's data that the concentrations of cadmium were considerably lower than in the accumulator industries referred to. At one working area he found average values for 8 hour working shifts over a 5-day period of from 13 to 89 μg Cd/m^3, at another place (two different positions) over a 9-day period, from 4 to 132 μg/m^3, and at a third working place (four different positions) over an 8-day period, from 1 to 270 μg/m^3. About 90 percent by weight of the particles had a size of less than 0.5 microns. It is obvious from the report that the mean exposure for the majority of the workers must have been considerably less than 0.1 mg Cd/m^3. Unfortunately the study did not show the earlier exposure conditions. King pointed out that during recent years, the working conditions in the industry had improved.

5.2.1.1.3 Respiratory effects not reported

Above have been discussed studies in which pulmonary effects of chronic cadmium intoxication have been observed. There are also reports with negative findings.

Suzuki, Suzuki and Ashizawa, 1965, examined workers exposed to cadmium stearate dust and lead in a vinyl chloride film plant. The study comprised 27 male workers in 1963 and 19 male workers (mean age: 22.8 years, S.D.:5.5 years, time of employment: 3.3 years, S.D.:1.9 years) as well as 24 controls in 1964. They found at the examination in 1964 no increased occurrence of respiratory symptoms in the exposed group compared to the controls. Furthermore, there was no difference between the two groups in the outcome of lung function tests. The concentrations of cadmium in 1963 (standard impingers) at one occasion (sampling time not given) were at four different operations 0.03, 0.26, 0.55 and 0.69 mg Cd/m^3. The size of the particles varied from 0.4 to 20 microns (cascade impactor, darc field microscopy). The exposure took place three or four times a day for twenty minutes each time. Nothing was mentioned about the use of respirators.

Apart from the above mentioned study, no reports are known to us in which a careful pulmonary examination, including lung function tests, has revealed negative findings. There are some reports, however, where the use of more insensitive methods has shown normal or only very slight changes. These reports are referred to below.

Princi, 1947, examined 20 workers in a cadmium smelter. In the clinical examination he found no subjective symptoms which could be connected with exposure to cadmium (no controls were examined). Pulmonary X-rays showed normal conditions. Lung function studies were not carried out. The average period of employment for the workers examined was 8 years (range: 0.5 to 22 years, 7 workers with more than 10 years). All of them were exposed to cadmium in the form of dust or fumes (CdO and/or CdS). Princi carried out air analyses on three different occasions at 11 different areas of work. In this connection he found values which, calculated as metallic cadmium, varied as a rule from 0.04 to 1.44 mg/m^3. In a few of the working areas there were considerably higher concentrations of dust. Thus in 2 places in which, to judge from the description of the working conditions, the men were probably exposed to cadmium sulphide, values of 19 and 31 mg Cd/m^3 were measured. In another area of work, where the workers were probably exposed to cadmium oxide, a content of 17 mg Cd/m^3 was measured. Since many of the men were stationed sometimes at the one, and sometimes at the other area of work, an accurate estimate of the individual exposure was not possible. Respirators were provided but worn infrequently.

Hardy and Skinner, 1947, left open the question of the possibility of chronic cadmium poisoning. They examined 5 workers exposed for periods from 4 to 8 years in the production of cadmium-faced bearings. The workers complained of unspecific symptoms, including respiratory symptoms on damp days. Chest X-rays were normal. No lung function tests were carried out. The authors gave the average exposure to cadmium as approximately 0.1 mg Cd/m^3 air.

L'Epée et al., 1968, examined 22 workers in an alkaline accumulator industry, 14 of whom had been employed for less than 5 years and 8 for more than 5 years. Unspecific respiratory symptoms were found among 5 workers. No pulmonary studies were made. The report included no quantitative data on cadmium exposure.

Tsuchiya, 1967, examined 13 workers (age range: 19 to 32 years) and 13 controls. The workers had been exposed to cadmium fumes while smelting alloys of silver and cadmium. No lung function tests were reported. Chest X-ray examinations did not reveal any abnormalities. No persistent subjective symptoms could be detected. The cadmium concentration in the air was reported as time weighted averages (electrostatic precipitator) at nose level of the workers for 5 days and values varying from 68 to 241 µg/m^3 were found.

5.2.1.2 Ambient air exposure

Only scanty data are available concerning a possible association between respiratory disorders and exposure to cadmium via ambient air. Lewis, Lyle and Miller, 1969, studied the cadmium, copper and iron concentrations in water-soluble protein fractions of liver extracts in connection with autopsies of patients with chronic bronchitis and emphysema. The samples were analyzed by atomic absorption spectrophotometry. They found a higher concentration of cadmium compared with a control group but no differences for iron and copper. The groups consisted of adult patients, but no age distribution was stated. For 20 patients with chronic respiratory problems, the cadmium concentrations had a mean of 40.4 (S.E.: 6.0) µg cadmium per g protein. The corresponding value for 38 controls was 10.6 (S.E.: 1.7) µg cadmium per g protein. Morgan (unpublished data) in a similar study also found an increased hepatic concentration of cadmium in deceased patients with a diagnosis of emphysema. For a discussion of this study, see section 7.2.

Peacock (unpublished data) reported a study of 127 residents, aged 50 to 69, of Birmingham, Alabama. They were given a detailed questionnaire on their health status supplemented by a medical examination, including determination of serum cadmium levels (atomic absorption, analyses carried out by Morgan). The 127 participants were part of a total sample of 464 individuals who in turn comprised 78 percent of those requested to attend. Peacock compared the prevalence of an extensive number of variables such as symptoms, food, drinking and smoking habits and social characteristics in groups of high and low cadmium values. The only statistically significant ($p < .05$) association he found, with vertigo, certainly was no more than would have been expected by chance. He also observed a relation ($p < .01$) between place of residence and cadmium levels, with most of the high serum cadmium levels among groups who might have been exposed to cadmium as an air pollutant presumably derived from the industrial steel complex in Birmingham. The study may serve as basis for further investigations with specified hypotheses.

In summary, there are a few data tending to show an increased cadmium storage in persons with a diagnosis of emphysema and/or chronic bronchitis at autopsies. No information concerning tha causes of the found association is available.

5.2.1.3 Prognosis

Friberg, 1950, showed that workers with emphysema had a poor physical working capacity. He also reported one fatal case in which the cause of death was a pronounced emphysema as well as another case in which pronounced pulmonary symptoms were present and hypertrophy of the right ventricular chamber was found at post mortem. Baader, 1951, reported one fatal case due to severe emphysema. From England reports of several cases in which the cause of death was emphysema have been published (Lane and Campbell, 1954, Bonnell, 1955, Smith, Kench and Smith, 1957, Smith, Smith and McCall, 1960 and Kazantzis et al., 1963). The British researchers have pointed out that they did not find evidence either clinically or pathologically of chronic bronchitis. Figure 5:3 shows a whole lung section of a fatal case.

The prognosis of chronic cadmium poisoning is further elucidated by data from two five-year follow-ups by Friberg and Nyström, 1952 and by Bonnell, Kazantzis and King, 1959, of the two earlier mentioned studies by Friberg, 1950, and Bonnell, 1955. When given respiratory function tests, exposed groups showed a greater deterioration with increase in age than the control group in the British study. The results in individual cases showed a deterioration in the men who had emphysema at the time of the original survey despite the fact that the majority with chronic cadmium poisoning had not been exposed to cadmium since the original examination. In the Swedish follow-up study, subjective symptoms increased in several of the cases. Though a general tendency toward poor lung function remained, further impairment had not taken place. Most of the workers had not been exposed to significant concentrations of cadmium during the period of the follow-up study.

5.2.2 In animals

Pulmonary changes have been found in animal experiments. Friberg, 1950, exposed 25 rabbits for 3 hours a day for 20 days per month for 8 months to about 8 mg cadmium iron oxide dust/m^3 (taken from the alkaline accumulator factory where the clinical studies were carried out, see section 5.2.1.1.1). This corresponded to approximately 5 mg cadmium/m^3, or about 900 min · mg/m^3 per exposure day. All rabbits showed signs of emphysema in addition to inflammatory changes. As the workers in the accumulator factory were exposed also to nickel graphite dust, similar animal experiments were carried out with such dust. Emphysema and inflammatory changes were seen but to a much lesser extent, despite the fact that the actual dust concentrations were 10 to 20 times higher than in the cadmium experiments.

Vorobjeva, 1957, installed intratracheally in rats cadmium oxide dust (0.25 mg/100 g bodyweight), cadmium iron dust (0.35 mg/100 g bodyweight) as well as nickel graphite dust (2 mg/100 g bodyweight). After 4 to 7 months the animals were killed. In the cadmium and cadmium iron groups there were signs of interstitial pneumonia, sclerosis and emphysema. Similar changes were not seen among the animals in the nickel graphite group. In a brief report from the U.S.S.R., Shabalina, 1968, mentioned that cadmium stearate did affect the lung tissue two months after an intratracheal installation. The studies were performed to evaluate symptoms of cadmium intoxication in human beings in the form of subatrophic cathars of the upper respiratory tract and hyposmia.

Against these findings stands a study by Princi and Geever, 1950. They exposed dogs to cadmium oxide dust (10 dogs, 6 hours a day, 5 days a week for 35 weeks) and cadmium sulphide dust (10 dogs, 6 hours a day, 5 days a week for about 30 weeks) without finding any respiratory changes at post mortem compared with a control group. The concentrations of cadmium in the air varied from 3 to 7 mg/m^3 with an average concentration of 4 mg/m^3. Ninety-eight percent of the particles were less than 3 microns in diameter. It should be mentioned that several of the animals had to be killed because of severe injuries received while fighting among themselves. Dogs that died of injuries had bronchopneumonia.

5.3 CONCLUSIONS

Brief inhalations of high concentrations of camium compounds can give rise to severe, often fatal, pulmonary changes (pulmonary oedema). This has been shown in human beings with regard to cadmium oxide fumes and in animals with regard to cadmium oxide fumes, cadmium chloride aerosols and cadmium oxide dust.

For human beings a fatal exposure to cadmium oxide fumes and cadmium chloride aerosols is not higher, probably lower, than about 2500 min · mg/m^3 (corresponding to about 5 mg/m^3 for 8 hours). An exposure to about 500 min · mg/m^3 (corresponding to about 1 mg/m^3 over 8 hours) is considered immediately dangerous.

Dose-response relationships for cadmium oxide dust are scarce and uncertain. In rabbits LD_{50} was about 8000 min · mg/m^3, which would correspond to about 15 mg cadmium oxide dust/m^3 for an 8-hour exposure.

Occupational exposure for longer periods of time to lower concentrations of cadmium compounds can give rise to chronic pulmonary disorders, characterized as emphysematous changes. These changes as a rule have taken several years to develop in human beings but have been observed already after a couple of years' exposure. Lung damage has been observed after exposure to cadmium oxide fumes as well as to cadmium oxide dust and cadmium pigment dust.

Dose-response relationships are very uncertain because time weighted averages are not available, or only available for short periods. Furthermore, it is not known what reduction of exposure was brought about due to the use of respiratory masks. There is reason to believe that cadmium oxide fumes are more dangerous than cadmium oxide dust. For cadmium oxide fumes, a prolonged industrial exposure to well below 0.1 mg/m^3 might well be considered hazardous, with reference to emphysema.

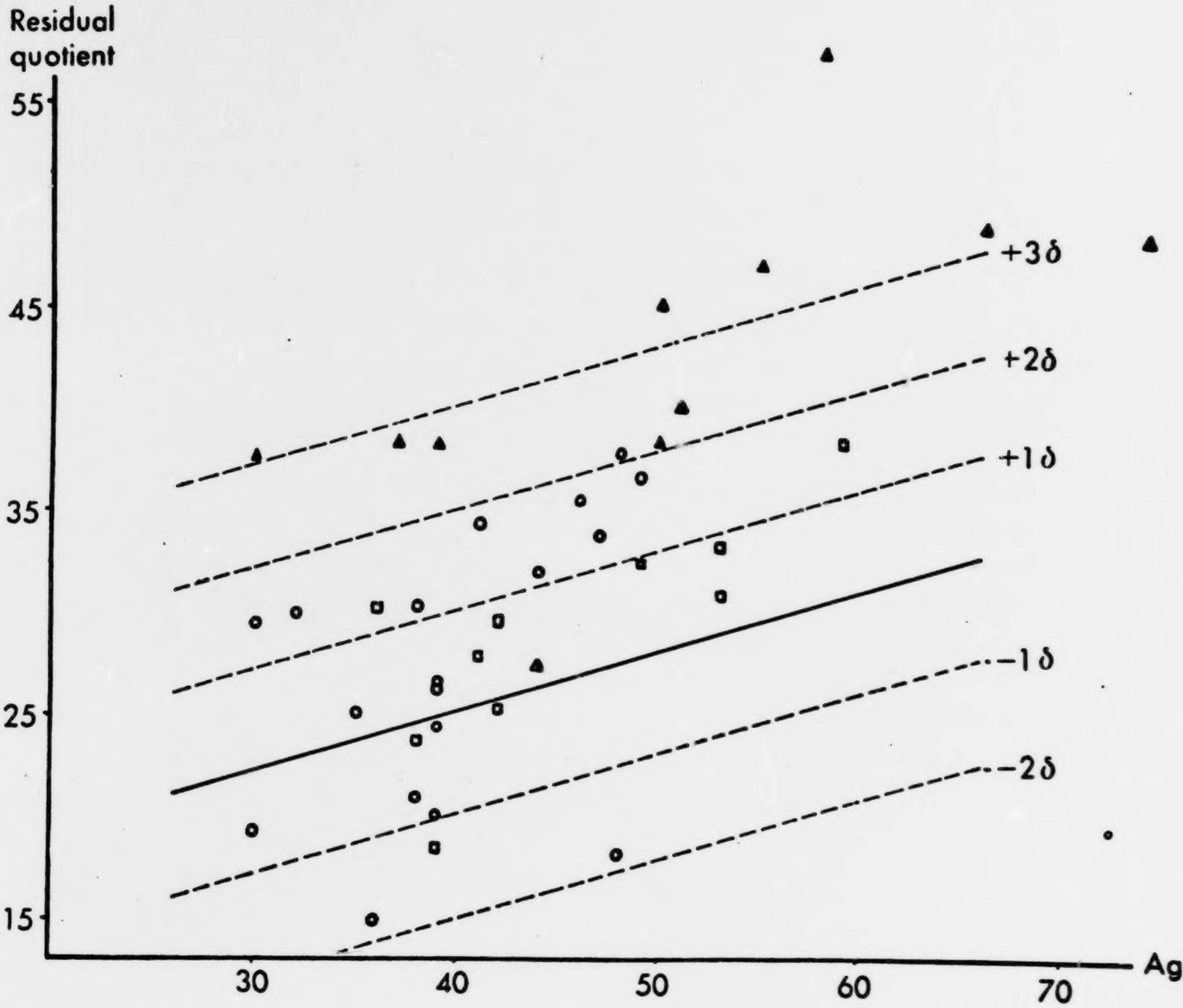
There exists evidence that non-occupationally exposed people with chronic bronchitis and emphysema have on an average a higher body burden of cadmium than "controls." No information on the cause of the found association is available.

Table 5:1 LD_{50} BY INHALATION OF ARCED CADMIUM OXIDE FUME FOR VARIOUS SPECIES

(from Barrett, Irwin and Semmons, 1947)

Time exposed: 10-30 minutes

Species	LD_{50} min · mg/m^3	Remarks
Rats	500	160 animals used in groups of from 10 to 25.
Mice	Less than 700. Probably about the same as for rats.	Approximate only.
Rabbits	2,500	"
Guinea Pigs	3,500	"
Dogs	4,000	"
Monkeys	15,000	"



Maximal physical working capacity with working test on bicycle ergometer:

▲ ≤ 600 kgm/min
○ = 900 kgm/min
□ ≥ 1,200 kgm/min

The regression line represents the mean residual quotient for 200 non-exposed workers.

The individual symbols represent exposed workers.

Figure 5:1 Lung Function (residual quotient) and Maximal Physical Working Capacity in Relation to Age in Workers Exposed to Cadmium Iron Oxide Dust (Friberg, 1950).

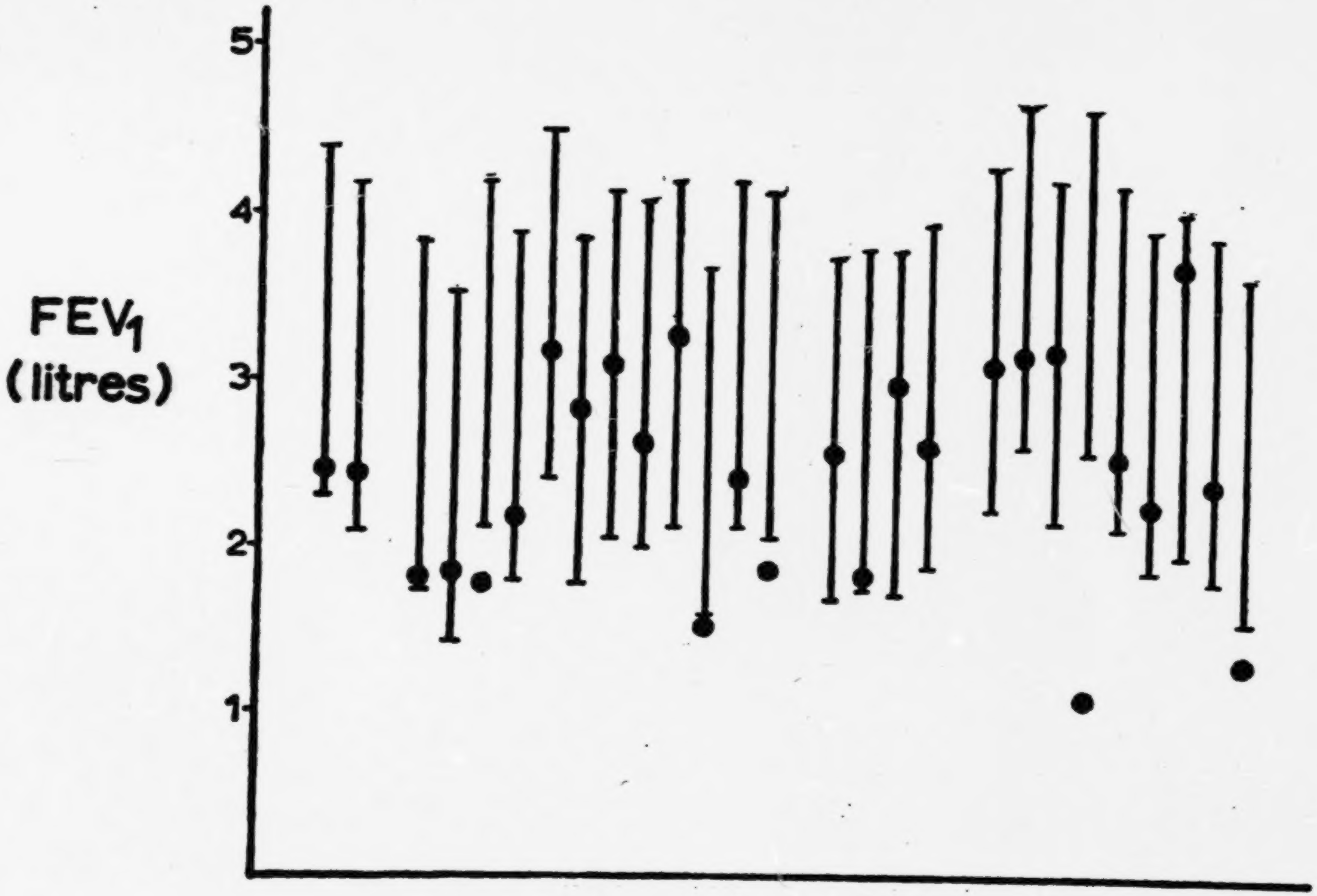


Figure 5:2 FEV$_1$ among Male Cadmium Workers in the Production of Alkaline Accumulators. The Normal Range for Men of the Same Age and Height (from Kory et al., 1961) Shown in Each Case (from Adams, Harrison and Scott, 1969).

NOT REPRODUCIBLE

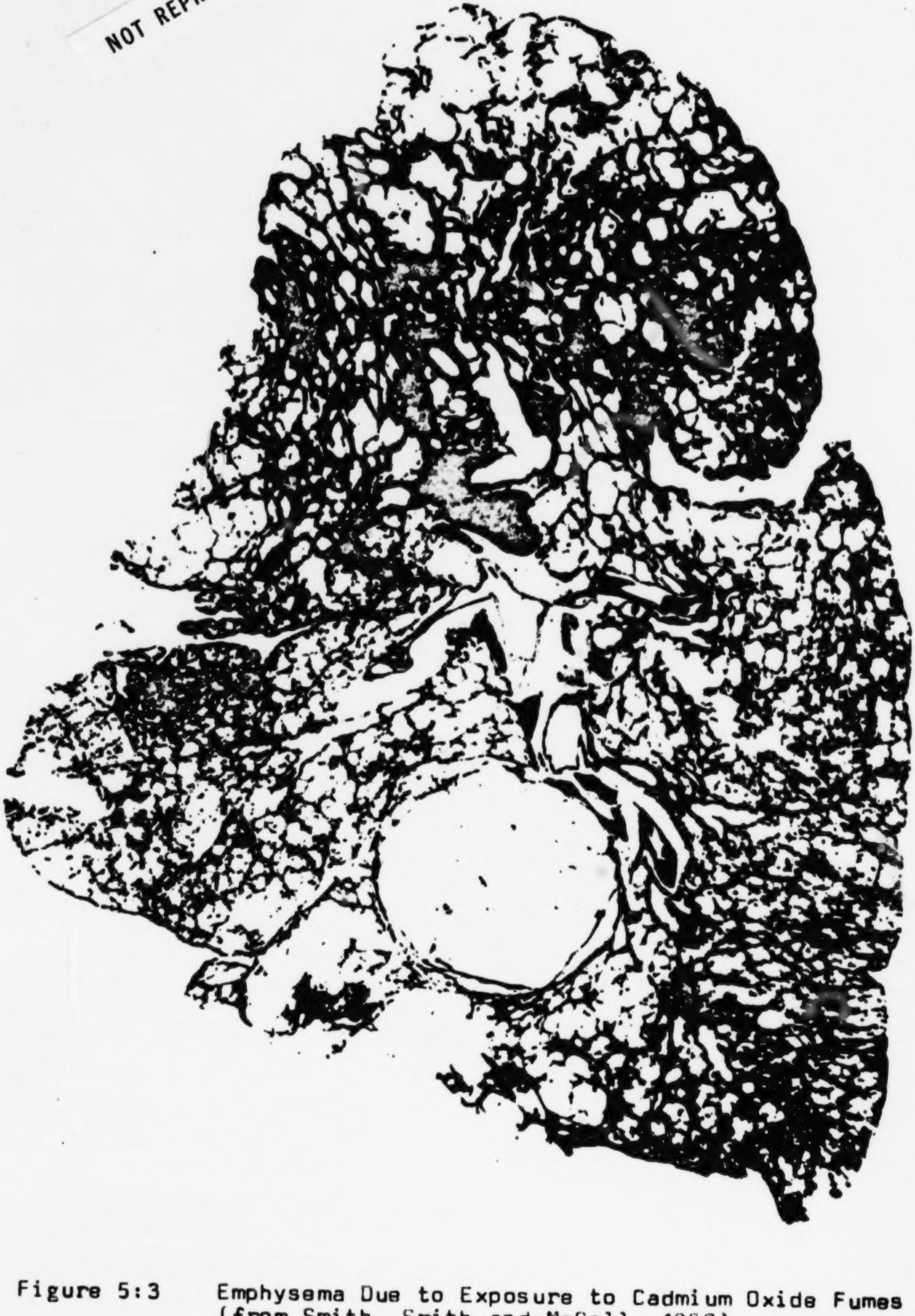


Figure 5:3 Emphysema Due to Exposure to Cadmium Oxide Fumes (from Smith, Smith and McCall, 1960).

CHAPTER 6

SYSTEMIC EFFECTS AND DOSE-RESPONSE RELATIONSHIPS

6.1 RENAL EFFECTS AND DOSE-RESPONSE RELATIONSHIPS

There is much evidence in the literature that exposure to cadmium will cause impairment of the kidneys. Investigations have covered workers exposed to different cadmium compounds in industry as well as animal experiments. Almost all of the effects referred to have resulted from prolonged exposure to cadmium. A brief mention of the acute effects will be made, particularly against the background of possible enhancement of the effects due to simultaneous exposure to chelating agents.

6.1.1 Acute effects and dose-response relationships

6.1.1.1 In human beings

Exposure to high concentrations of cadmium oxide fumes has caused severe acute lung damage (see section 5.1). In two fatal cases described by Bulmer, Rothwell and Frankish, 1938, "Cloudy swelling" was found in the kidneys at microscopic examination. The authors ascribed this to a general toxemia. Beton et al., 1966, reported on a fatal case in which bilateral cortical necrosis of the kidneys was found at autopsy. They thought that this was mainly due to vascular changes associated with massive pulmonary changes. The concentration of cadmium in the kidneys was given as 5.7 ppm wet weight, which is below the average "normal" level for people of the patient's age (53 at death).

In two other patients, who recovered after exposure, transient proteinuria was noted. Electrophoretic examination of the urine from one patient showed that mainly albumin was excreted. These data on renal effects in man do not allow any conclusions regarding the direct action of cadmium on the kidneys after acute exposure, as the general metabolic disturbances caused by the pulmonary oedema and accompanying pneumonia probably will overshadow any other effects.

6.1.1.2 In animals

Acute effects of inhalation of cadmium have been studied on cats by Prodan, 1932. Two cats were exposed to high concentrations (precise amount not stated) of cadmium oxide fumes for 30 minutes. One of them showed fatty degeneration, especially in the convoluted tubules. In another experiment three cats were exposed for 24 hours to cadmium oxide fumes. The concentration of cadmium in air at the beginning of the exposure, 18 mg/m^3, was gradually reduced to 4 mg/m^3 at the end of the experiment. The cats were killed 5 and 9 days after exposure. Histological examinations disclosed in all three a moderate amount of fat in the tubular epithelium. It was calculated that the cats had inhaled between 6 and 12 mg of cadmium.

Regarding the dose-response relationship after respiratory exposure, no certain conclusions can be drawn, as in these experiments the lung lesions were dominant and might have caused a general toxemia. As severe, probably lethal, lung damage will occur at cadmium concentrations which can not cause renal damage, the kidney is not a critical organ after acute exposure.

Experiments involving a subcutaneous injection have revealed that the kidneys were not damaged when rats were given soluble cadmium salts (2.2 mg Cd/kg), a dose which did cause testicular necrosis (Parízek and Zahor, 1956, Parízek, 1957, 1960, and Kennedy, 1968). Favino and Nazari, 1967, observed tubular lesions of the nephrotic type in rats given a single subcutaneous injection of cadmium chloride (10 mg Cd/kg).

In the rabbit, Foster and Cameron, 1963, produced renal lesions with 2 subcutaneous injections of cadmium chloride (9 mg Cd/kg). The most striking changes were found in the proximal tubules.

6.1.1.3 Influence of chelating agents

It has earlier been said that the treatment of cadmium poisoning will not be reviewed. However, some chelating agents (e.g. EDTA and NTA) have been introduced as components of detergents. A possible role of these agents in changing the toxicity of cadmium in man's environment has been discussed. As most of the work on chelating agents is concerned with more or less acute effects of cadmium, a brief mention of a few chelating agents will be made in this section.

In 1946, Gilman et al. documented a decrease in the acute mortality normally incurred after a single injection of cadmium when rabbits were treated with 2,3-dimercaptopropanol (BAL). However, several of the rabbits succumbed later from kidney damage. In a follow-up of these studies, Tepperman, 1946, showed that BAL increased the uptake of cadmium in the kidneys, an observation confirmed by Niemeier, 1967. Also EDTA has been shown to decrease the acute lethality from a single injection of cadmium (Friberg, 1956, and Eybl, Sýkora and Mertl, 1966a) whereas the agent increased the nephrotoxicity of cadmium after repeated exposure to cadmium (Friberg, 1956). Dalhamn and Friberg, 1955, have presented evidence of a similar unfavorable effect of BAL upon cadmium toxicity during prolonged exposure.

Tobias et al., 1946, showed that prophylactic treatment with BAL had a deleterious effect upon mice exposed to cadmium chloride dust by inhalation. However, when BAL was given promptly after exposure to the Cd-dust, in an optimal course of repeated injections, it could reduce the mortality considerably. Also in these experiments BAL increased the cadmium content of the kidneys, but this seems not to have been of importance for mortality or pathological changes, as no renal pathology was observed following BAL-treatment of mice poisoned by inhaling cadmium.

All of the experiments performed by Tobias et al. consisted of a short, single exposure. When the data by Gilman et al., Tepperman and Dalhamn and Friberg are considered together with what is known about renal lesions as a main feature of chronic cadmium poisoning, it is highly probable that BAL also increases the toxicity of inhaled cadmium during long-term exposure.

Chelating agents such as hydroxyethylene diaminetriacetic acid (HEDTA), diethylenetriaminepentaacetic acid (DTPA) and others also had a preventive effect upon acute cadmium toxicity. Both EDTA and DTPA (Eybl, Sýkora and Mertl, 1966a) treatments decreased the uptake of cadmium in the kidneys. However, to what extent the decrease in uptake meant a decrease in toxicity in the kidney is not known.

In some contrast to the above mentioned diminuations in acute toxicities of injected cadmium, Chernoff and Courtney, 1970, reported an increased acute toxicity and increased fetal mortality in rats given a single injection of a chelate of cadmium with nitrilotriacetic acid (NTA). However, the preliminary nature of their information makes an evaluation of these findings difficult. Long-term toxicity has often been influenced in a manner different from acute toxicity by therapy with chelating agents. It is of great importance to investigate the influence of NTA and other chelating agents on long-term toxicity of cadmium.

6.1.2 Chronic effects and dose-response relationships

6.1.2.1 In human beings

6.1.2.1.1 Proteinuria and renal function

In 1950 Friberg, having investigated a large group of workers exposed to cadmium oxide dust in an accumulator factory (for further details see section 5.2.1.1.1), showed that prolonged exposure to cadmium gave rise to renal damage. He studied two groups, one of 43 workers with a mean exposure time of 20 years (range: 9-34 years) and one of 15 workers with a mean exposure time of 2 years (range: 1-4 years). In the former group proteinuria could be demonstrated with the nitric acid test in 65 percent of the workers and with the trichloracetic acid test in 81 percent. However, only 11 percent of the nitric acid positive urines reacted positively to the picric acid test. In the other group, with the mean exposure time of two years, no positive reactions were obtained with any of the tests. Tests of renal function disclosed that in the first group, 21 percent (9 out of 42) had decreased ability to concentrate the urine (maximum specific gravity ≤ 1.019). Out of those 9 people, 8 had a constant proteinuria. In 33 workers with a higher concentration capacity (maximum specific gravity ≥ 1.020), only 11 (33%) had a constant proteinuria.

As the proteinuria differed from ordinary albuminuria concerning precipitation reactions, a special investigation was made (Olhagen, 1950). Using electrophoretic and ultracentrifugal analysis, Olhagen found that in the urinary proteins the amount of albumin was relatively small and that the dominating proteins migrated as α-globulins. The molecular weight for the main component was between 20,000 and 30,000.

Friberg, 1950, concluded that prolonged exposure through inhalation of cadmium oxide dust gave rise to, as a rule, relatively mild kidney damage. He suggested that the kidney injury was secondary to the excretion of low molecular weight proteins.

As late as 1947 Princi had claimed that prolonged exposure to cadmium did not constitute any serious health hazard. Having investigated 20 smelter workers who had been exposed to different cadmium compounds during a range of 1 to 20 years, he found no proteinuria. As he had used the boiling test (personal communication), proteinuria would not have been detected. Friberg in 1950 and Piscator in 1962b showed that urinary proteins from cadmium workers were not precipitated with this test. The studies by Princi thus did not prove that renal damage had not occurred.

In 1950 Friberg described the common findings of proteinuria in workers in alkaline accumulator factories also in Germany, England and France. Further evidence for the high prevalence of proteinuria in cadmium workers has been provided by Baader in 1951, Smith, Kench and Lane in 1955, Bonnell in 1955, Smith and Kench in 1957, Bonnell, Kazantzis and King in 1959, Kazantzis et al. in 1963, Potts in 1965, Suzuki, Suzuki and Ashizawa in 1965, Tsuchiya in 1967, and Adams, Harrison and Scott in 1969. From these investigations, it is seen that not only cadmium oxide dust, but also cadmium oxide fume, cadmium sulphide and cadmium stearate may give rise to proteinuria, provided exposure has been prolonged. That proteinuria could appear after the workers had been removed from exposure has been indicated by the findings of Friberg and Nyström in 1952. They re-examined 38 workers and found proteinuria in 4 who had earlier had negative test results.

In many of the above mentioned investigations only qualitative tests had been used for detecting proteinuria. First when quantitative determinations were performed by Piscator in 1962a and b was it possible to study protein excretion in more detail in relation to exposure times and removal from work. In 1962a Piscator studied a group of 40 workers, of whom 39 had been included in Friberg's investigations in the 1950 report. By using a quantitative method for the determination of the total urine protein, Piscator, 1962a, has shown that in these workers, who had not been exposed to cadmium for the last 10 years, there was a relationship between the exposure times, i.e., total dose, and protein excretion, as shown in figure 6:1. Fourteen urine samples were examined half a year later by Piscator, 1962a. Essentially the same protein excretion values were obtained, indicating that this proteinuria was constant. In additional follow-ups it was found that, in 18 workers reexamined in 1963, (Piscator, 1966a) and in 27 workers reexamined in 1969 (Piscator, unpublished data) from the above mentioned group of 40 workers, the protein excretion was in most cases virtually unchanged 3 and 10 years after the first quantitative determinations in 1959. As Friberg had not used a quantitative method for the determination of protein, a similar comparison could not be made with his original results. However, a comparison was made between the results of nitric acid and trichloracetic acid tests from the two investigations. No marked changes had occurred in the group (Piscator, 1962b).

Proteinuria has thus been a common finding in cadmium workers. Further evidence of a disturbed renal function has been given by the findings of glucosuria documented by Bonnell, Kazantzis and King, 1959, Smith, Wells and Kench, 1961, Kazantzis et al., 1963, Suzuki, Suzuki and Ashizawa, 1965, Piscator, 1966a, and Adams, Harrison and Scott, 1969. Amino-aciduria has been observed by Clarkson and Kench, 1956, Kazantzis et al., 1963, Piscator, 1966a, and Adams, Harrison and Scott, 1969. A decreased concentrating capacity was detected by Friberg, 1950, and by Ahlmark et al., 1961. Kazantzis et al., 1963, and Adams, Harrison and Scott, 1969, found changes also in renal handling of uric acid, calcium and phosphorus. Proteinuria can appear alone without the other above mentioned changes, indicating that proteinuria is often one of the earliest signs of cadmium intoxication.

Though glomerular function has not been extensively investigated, the studies of Friberg, 1950, Ahlmark et al., 1961,and Adams, Harrison and Scott, 1969 have shown that decreases in glomerular filtration rates will appear in cadmium workers. This symptom is rather late, appearing after the other above mentioned changes which are more indicative of tubular dysfunction. Kazantzis et al., 1963, found profound changes in tubular function but no definite evidence of glomerular malfunction.

There have been several deaths due to chronic exposure to cadmium. However, almost invariably, the primary cause of death has not been kidney disease, which is in agreement with the findings that proteinuria is usually constant for many years, with no marked progress of renal dysfunction once exposure has ceased.

6.1.2.1.2 Nature of proteinuria

In 1958 Butler and Flynn described the so-called tubular proteinuria which they found in cases with tubular dysfunction, as in the Fanconi syndrome, galactosemia, etc. This proteinuria was characterized by a relatively small albumin fraction and dominance of proteins with mobility as α-, β- and γ- globulins in paper electrophoresis. By comparing urinary proteins from cadmium workers with urinary proteins from persons with other tubular disorders, Butler and Flynn, 1961, Butler et al., 1962, Piscator, 1962a, and Kazantzis et al., 1963, were able to show that the proteinuria in chronic cadmium poisoning was similar to the tubular proteinuria described by Butler and Flynn in 1958. Typical patterns of urinary proteins in chronic cadmium poisoning are shown in figure 6:2. Further investigations by Piscator, 1966a and b, showed that the proteins excreted by cadmium workers were composed mainly of low molecular weight proteins, chiefly derived from the serum. Among these were low molecular weight β_2- microglobulin enzymes such as muramidase and ribonuclease and immune globulin chains, the latter constituting nearly half of the low molecular weight fraction. It was not possible to show the existence of any proteins specific for cadmium poisoning.

Most researchers now accept that the early proteinuria in chronic cadmium poisoning is of the tubular type and caused by decreased reabsorption of proteins (Harrison et al., 1968, Davis, Flynn and Platt, 1968, Berggård and Bearn, 1968, Peterson, Evrin and Berggård, 1969, and Rennie, 1971). However, Smith, Wells and Kench in 1961 found in urine protein from two cases of chronic cadmium poisoning a low molecular weight albumin, immunologically indistinguishable from normal serum albumin but with a considerably lower molecular weight. They introduced the word "mini-albumin" for this protein which they considered the main feature of chronic cadmium poisoning. Since their conclusions were founded upon investigations of only two samples, lyophilized and stored for 8 years at room temperature before examination, further data are needed. (see also section 6.1.2.2, however). Using the same methods, Piscator (unpublished data) could detect a small quantity of albumin in low molecular weight fractions obtained by gel filtration from the urine of both normal men and workers with chronic cadmium poisoning. Piscator considered this due to the "tailing" of ordinary albumin on the Sephadex column.

Vigliani, Pernis and Luisa, 1966, using specific anti-sera, demonstrated that some 30 percent of the protein in the urine from 3 Swedish cadmium workers consisted of L chains of γ-globulin. These findings do not contradict the above mentioned findings by Piscator despite the fact that Vigliani interpreted his results as unfavorable to cadmium proteinuria's being simply an increased normal proteinuria caused by impaired tubular reabsorption. In their first report, Vigliani, Pernis and Luisa, 1966, expressed the opinion that cadmium proteinuria is mainly caused by a defect in the assembling of polypeptide chains of immunoglobulins, resulting in the excretion of low molecular weight chains. Recently, in 1969, however, Vigliani abandoned this theory in favor of the hypothesis that cadmium has an effect upon the catabolism of immunoglobulins and other proteins in the kidneys.

6.1.2.1.3 Renal stones

Especially in workers in Sweden, the formation of renal stones has been a common feature (Friberg, 1950, and Ahlmark et al., 1961). Ahlmark et al., 1961, found that 44 percent of a group of workers exposed to cadmium dust for more than 15 years had a history of renal stones. In 1963, Axelsson reported that the stones were mainly composed of basic calcium phosphate. He stated that the formation of such stones was evidence of a disturbed metabolism of calcium and phosphorus.

During later years, kidney stones have also been found in British accumulator factory workers by Adams, Harrison and Scott, 1969. It is noteworthy that both this later research group and Axelsson in 1963 found a higher prevalence of renal stones in non-proteinuric men, indicating that more developed tubular dysfunction means less risk of developing kidney stones. This finding also indicates that changes in reabsorption of calcium might occur early. Adams, Harrison and Scott, 1969, stated that some of their workers had hypercalcuria without proteinuria.Kazantais (personal communication) has recently found renal stones in three out of twelve workers previously referred to (Kazantzis et al., 1963).

6.1.2.1.4 Autopsy and biopsy findings

Information is available from a total of 11 autopsies (6 exposed to cadmium oxide dust and 5 to cadmium oxide fume) and 9 biopsies (all exposed to cadmium oxide dust). In table 6:1 data are given from 6 autopsies and 9 biopsies on workers exposed to cadmium oxide dust. In four of the autopsy reports (S.W.H., K.J., H. B., and A.B.) the morphological changes in the kidneys were mainly confined to the proximal tubules, whereas the glomeruli were less affected. Similar but less pronounced changes were seen in two biopsies. In the other cases with morphological changes, the exact nature of these has not been specified. The data in the table indicate that cadmium levels were lower in cases with morphological changes than in cases without detectable morphological alterations, or with only minor changes. As exposure times were longer in the former cases and the concentrations of cadmium dust conceivably higher (after 1950 improvements in working conditions were made in the Swedish factory), the lower levels in these cases can not be explained by less exposure. There is some difference between the two groups in regard to the time which had elapsed between the end of exposure and autopsy or biopsy. This fact does not seem to have been of significance, though, as can be seen if patients examined different times after the end of exposure are compared. The combination of heavy exposure to cadmium, severe renal damage and relatively low levels of cadmium in the kidneys indicates instead a considerable excretion of cadmium. In workers with no impairment or only minor dysfunction (latter group), the renal losses must have been smaller and thus the renal levels of cadmium were higher.

The above mentioned findings in workers exposed to cadmium oxide dust are further supported by data from autopsies on workers exposed to cadmium oxide fumes. Smith, Smith and McCall, 1960, reported on autopies on 4 workers exposed for less than 10 years. The autopsies were performed 5-18 years after the last exposure. These workers had been removed from exposure because of respiratory symptoms. Proteinuria had been the only sign of renal impairment in three of them. Histological examination did not reveal any renal alterations. Cadmium levels in the cortex were between 150 and 395 ppm wet weight, i.e., in the same range as in workers exposed to dust and without major renal changes. Bonnell, 1955, on the other hand, reported on a worker exposed for 32 years to fumes and autopsied only 2 years after the last exposure. There was severe renal damage with both tubular and glomerular involvement. The cadmium concentration in cortex was relatively low, 62 ppm wet weight.

In animal experiments (section 6.1.2.2) it has been shown that morphological changes became evident and renal levels of cadmium ceased to rise after a certain period of exposure. Further exposure then resulted in a lowering of the cadmium concentration. These findings agree with the findings in exposed workers.

In conclusion, when a cadmium worker suffers severe renal damage through the toxic action of cadmium, his kidney concentration of cadmium will decrease considerably. Thus, he will have lower levels in kidneys than a worker with only slight renal disturbances.

6.1.2.2 In animals

Prodan, 1932, stated that renal lesions consisting of fatty degenerations in the tubules developed in cats given daily oral doses of 2, 10 and 100 mg of cadmium for 1-2 months. However, controls were not included in the experiment and no certain conclusions can be drawn from these results. Wilson, deEds and Cox, 1941, added cadmium chloride to the diets of rats in concentrations of 31, 63, 125, 250 and 500 ppm. Exposure time was 100 days, after which the rats were killed. Histological examination showed slight tubular changes and no glomerular alterations in the animals exposed to 63 ppm cadmium in the diet and no changes in animals exposed to 31 ppm cadmium. Cadmium determinations were not performed on the kidneys.

In 1950 Princi and Geever reported that they could not find evidence of morphological changes in the kidneys of dogs subjected to prolonged exposure to cadmium oxide dust or cadmium sulphide. (average concentration: 4 mg Cd/m^3). They made routine analyses of urine but used only the boiling test, and did not detect protein. In 1950, Friberg made a long-term experiment (for details, see 5.2.2) in which he exposed rabbits for 3 hours a day for 28 days per month for 8 months to about 8 mg cadmium iron oxide dust/m^3. After 4 months of exposure, moderate proteinuria could be demonstrated with the trichloracetic acid test. When the animals were killed after 7-9 months of exposure, histological examination did not disclose any structural changes. Cadmium concentrations in the kidneys were generally between 300 and 700 ppm wet weight. When a group of rabbits was given subcutaneous injection of cadmium sulphate, 0.65 mg Cd/kg, 6 days a week, proteinuria was demonstrated after 2 months. Analyses of cadmium in the kidneys were not performed. Electrophoretic analysis of urine proteins showed that the main component was not the same as the one found in rabbits with kidney damage due to uranium salts. In further experiments, Dalhamn and Friberg, 1957, found that mainly tubular changes took place in rabbits injected with cadmium, whereas the glomeruli were not affected.

Bonnell, Ross and King, 1960, gave rats of both sexes an intraperitoneal dose of cadmium chloride (0.75 mg Cd/kg) thrice weekly (for details see 4.2.2.2). After 5-6 months, injections were discontinued for 1-2 months. Thereafter, some animals were given a reduced dose, while others were given no further injections. The total time for the experiment was one year. Every month animals were killed and histological examinations performed. After 4 months of exposure, tubular damage was evident. From that time despite continued exposure there was no further increase in kidney levels of cadmium; in fact, some decrease in kidney concentration could be demonstrated (see figure 4:10). After 4 months the renal concentration of cadmium was about 275 ppm wet weight and after 5 months, about 225 ppm. The corresponding concentrations in cortex would be about 400 and 325 ppm, respectively.

These data are in accord with the findings by Friberg, 1952. He could show that rabbits given daily subcutaneous injections of radioactive cadmium sulphate had very low urinary excretion of Cd during the first two months, while after 2 months of exposure, the cadmium excretion abruptly increased 50-100 fold (see figure 4:11). After one month of exposure the renal concentration of cadmium was on an average 126 ppm wet weight whereas after 2 1/2 months of exposure the average concentration was 213 ppm. Friberg reported also that the concentration in cortex was about 5 times higher than in medulla which means that in cortex the concentrations would have been about 200 and 350 ppm, respectively, under the assumption that the mass of cortex is equal to or slightly larger than that of the medulla. In later experiments, Friberg, 1955, alternating radioactive and nonradioactive cadmium, demonstrated that a large part of the excreted cadmium must have come from deposits in the kidneys.

Axelsson and Piscator, 1966a, gave rabbits subcutaneous injections of cadmium chloride, 0.25 mg Cd/kg 5 days a week. After 17 weeks, alkaline phosphatase activity of the renal cortex decreased. After 23 weeks there was a decrease in the capacity to reabsorb glucose, together with considerable proteinuria and excretion of cadmium. Histological examination (Axelsson, Dahlgren and Piscator 1968) revealed that already after 11 weeks mild alterations took place in the proximal tubules. At that time cadmium concentration in the renal cortex was about 250 ppm wet weight (range: 194-315). After 23 weeks, pronounced changes were found not only in the proximal tubules, but also in other parts of the nephron. The collecting tubules were not detectably affected. Though the glomeruli showed some slight alterations in some cases, most cases were without demonstrable alterations.

In another group of rabbits, exposure conditions were similar to those stated above, but exposure was discontinued after 24 weeks, after which the animals were followed for another 30 weeks. Urine investigations showed that protein excretion was significantly higher than in controls after 12 weeks of exposure, with a maximum at about one month after exposure had ceased. Then came a reduction in protein excretion. At the end of the observation time, there was no significant difference between exposed animals and controls. Electrophoretic examination of urinary proteins showed a predominance of proteins with a mobility as α- and β-proteins. It was concluded that this corresponded to the tubular proteinuria found in human beings. Before these animals were killed, kidney function was investigated.

After death, alkaline phosphatase activity and cadmium in renal cortex were determined, as described by Axelsson and Piscator, 1970. Glucose reabsorption and protein excretion did not differ significantly between exposed and control animals. However, a highly significant decrease in the activity of alkaline phosphatase was found. The renal cortex in the exposed animals contained large amounts of cadmium, about 250 ppm wet weight, despite the fact that the rabbits had been without exposure to cadmium for 30 weeks (see also 4.2.2.2). Morphologically, there was an almost complete regeneration of the tubular epithelium. It was concluded that in the rabbit, exposure to cadmium would give rise to renal tubular damage, partly reversible, as judged by functional and morphological investigations.

It was mentioned earlier (section 6.1.2.1.2) that Kench and coworkers have reached the opinion that the excretion of a low molecular weight albumin is the main feature of the proteinuria in chronic cadmium poisoning in man. In experiments on rabbits (Kench, Wells and Smith, 1962), on monkeys (Kench, Gain and Sutherland, 1965, and Kench and Sutherland, 1966), and on rats (Kench and Sutherland, 1966), they were able to isolate an albumin of low molecular weight (10,000) from urine. In these experiments, however, animals were given very large doses of cadmium by intravenous injections (2 mg/kg twice a week) or a single intraperitoneal injection (15 mg/kg). Thus, the experimental conditions did not reproduce the slow chronic cadmium poisoning in man. At present, these experiments are indicative that large doses of cadmium may cause profound changes in protein metabolism. More evidence is needed before these experimental results can be applied to chronic cadmium poisoning in man.

In some reports, such as those by Princi and Geever in 1950 and by Anwar et al. in 1961, no effects on the kidneys were reported, despite prolonged exposure to cadmium. Princi and Geever stated that "in no case was tubular damage found in the kidneys (such as might be expected from severe metal poisoning)." Milder tubular lesion, often reported in chronic cadmium poisoning, might not have been registered. Princi and Geever found relatively large amounts of cadmium in the blood (38-119 μg/100 g whole blood) and urine (32-382 μg/liter) of dogs exposed to cadmium oxide dust and, to some extent, in dogs exposed to cadmium sulphide. However, kidney levels were low, in the same range as those for normal human beings. On the other hand, large amounts of cadmium were found in the liver (12-47 ppm in dogs exposed to cadmium oxide), bile and feces. The authors do not mention whether the values are calculated as ppm wet weight or dry weight. We have assumed that they are wet weight values.

Anwar et al. gave a total of 8 dogs cadmium in drinking water for 4 years in concentrations ranging from 0.5-10 ppm. One additional dog was used as control. They stated in their summary that pathological changes were not produced in dogs receiving cadmium. However, in their textual discussion, they described the findings of larger amounts of fat in the proximal convoluted tubules and in some areas, atrophied tubules, in one dog from each of the two groups receiving the higher concentrations (2 dogs: 5 ppm, 2 dogs: 10 ppm). As the authors thought that some animals also were infected with Leptospira, they concluded that some of the changes might be due to leptospirosis. Because of the small number of dogs used, the data are of limited value and in any case can not be taken as evidence that long-term exposure to orally ingested cadmium will not give rise to kidney damage.

6.1.2.3 Mechanisms for the development of the renal injury

It has been shown that cadmium will accumulate in the kidneys. During the period of accumulation, only small amounts of cadmium will be excreted in the urine, whereas, when a certain concentration has been reached in the kidneys, cadmium excretion will increase and renal levels will remain the same or decrease.

A hypothesis on the development of renal injury as advanced at our institute will now be set forth. In section 4.2.8 it was said that cadmium is probably transported to the tubules bound to the low molecular weight protein, metallothionein. During normal conditions this protein will be reabsorbed in the tubules just as other proteins, and cadmium will accumulate in the renal tissue. Cadmium excretion in "normal" people and in workers with short periods of exposure to cadmium is thus low because proteins are almost completely reabsorbed. With increasing exposure, more cadmium than can be bound by metallothionein will eventually be accumulated in the kidneys. Cadmium will then exchange with zinc in enzymes necessary for reabsorption and catabolism of proteins. Chiappino, Repetto and Pernis, 1968, found inhibition of the leucine-aminopeptidase activity in the renal cortex of cadmium exposed rats and in rabbits exposed under similar conditions as in the experiments by Axelsson and Piscator in 1966a. Leucine-aminopeptidase is a zinc-dependent enzyme thought to play a role in the renal handling of proteins. As a result of these antienzymatic actions less protein will be catabolised or reabsorbed, causing tubular proteinuria. Cadmium excretion will increase as also less metallothionein will be reabsorbed. At this stage the accumulation rate of cadmium will become slower, but cadmium will still be reabsorbed and cadmium levels in the tissue may get still higher. The reabsorption defect will be greater and eventually renal cadmium will cease to increase. Tubular cells will be damaged by cadmium and it is conceivable that cadmium will be excreted together with desquamated tubular cells, resulting in a decrease in renal levels of cadmium. If glomerular function is impaired, there will also be less filtration of metallothionein.

What has been described above might be true in continuous exposure. If exposure is discontinued when there is slight or no proteinuria, there is a possibility that cadmium levels in kidneys will increase for some time, probably depending upon liver levels. Proteinuria may thus appear some time after exposure has ceased, as supported by findings in workers removed from exposure (Friberg and Nyström, 1952) and in animals (Axelsson and Piscator 1966a). The mechanisms mentioned above might also explain the poor correlations between proteinuria and cadmium excretion in workers (Smith and Kench, 1957), as the former will depend mainly on the tubular dysfunction while the latter will depend upon both this dysfunction and the amount of metallothionein produced in the body, which in turn will depend upon recent exposure.

The findings in autopsy cases of chronic cadmium poisoning and in biopsies from exposed workers presented a paradox, i.e., high levels of renal cadmium were combined with histologically normal kidneys while relatively low cadmium levels were combined with long-standing proteinuria and gross structural changes in the kidneys. The above mentioned mechanisms will explain this paradox, i.e., the more severe and long lasting the renal lesion, the more cadmium will be excreted.

6.1.2.4 Dose-response relationships

In order to evaluate dose-response relationships, concentrations of cadmium in the kidneys at different effect levels would probably be the most valid information. Seemingly less valid factors - exposure through food and air , or concentrations in blood and in urine-will first be discussed.

6.1.2.4.1 Evaluations starting from data on exposure in the environment

The amount of cadmium that gives rise to kidney damage can theoretically be evaluated from data on environmental exposure (concentrations in food, water, industrial or ambient air) in relation to effects. Unfortunately, available data are too inadequate to provide quantitative evaluations of the dose. Workers in industries, for example, have often been exposed for decades. Determinations of cadmium in air, on the other hand, have been performed only occasionally, and often show that exposure varies considerably within the same working place. Measurements in the breathing zone of the workers have seldom been performed. Further, the use of respirators may change the exposure situation considerably. The long-term evaluation of excessive exposure via ingestion of cadmium is hindered by similar problems, as exemplified in Chapter 8, where the Itai-itai disease in Japan is discussed.

6.1.2.4.2 Evaluations starting from data on cadmium concentrations in blood and urine

As can be realized from the detailed discussion in section 4.4, cadmium levels in blood and urine are of very limited value for evaluating dose-response relationships. Blood levels can not be used for estimating renal levels because they might vary considerably during exposure, while the kidneys will accumulate cadmium continuously up to a certain level (when damage will occur). Though increased blood levels show that exposure has taken place, it will be impossible to differentiate whether they reflect accumulated cadmium or recent exposure.

Neither can cadmium concentrations in urine be used, as during the period the kidneys are accumulating cadmium, there is not a corresponding increase in urinary excretion of cadmium. When an increase in urinary cadmium levels can be seen, renal dysfunction will have already taken place (Section 4.4.).

6.1.2.4.3 Evaluations starting from data on cadmium concentrations in the kidneys

In table 6:1 data are given on workers industrially exposed for long periods to considerable amounts of cadmium. As can be seen, the concentrations of cadmium in the renal cortex have varied within wide ranges. In section 6.1.2.1.4 it was concluded that the low values found in workers with morphologically pronounced kidney damage resulted not from low exposure but from high excretion of cadmium. In table 6:1 there can also be seen a group of workers with long exposure to cadmium but with no or only slight morphologically detectable kidney damage. Only some of them had proteinuria. It can be assumed that the kidney levels of cadmium in such a group would be fairly representative for concentrations at the time at which the first signs of renal dysfunction appeared. Reported levels in such cases did, with one exception, vary between 150-450 ppm wet weight in renal cortex.

In the experiments on rabbits and rats (section 6.1.2.2) functional and morphological changes appeared when the cadmium concentration in the renal cortex reached about 200-400 ppm wet weight. Renal levels of about 130 ppm wet weight, corresponding to about 200 ppm wet weight in renal cortex (only one-month observation time), were found in rabbits with neither proteinuria nor excretion of cadmium. The animal experiments thus suggest that about 200 ppm wet weight is a critical concentration in the cortex.

Even if animal data are not immediately valid for man, it is striking that they are within the range for human beings exposed to cadmium for several years and with slight or no impairment. It is considered justified to start out from a value of 200 ppm cadmium in renal cortex (wet weight) when discussing which exposures can bring about cadmium-induced detectable renal dysfunction in man. It should be strongly emphasized that with renal dysfunction is here meant a dysfunction that has been detected with fairly crude methods. With all probability cellular effects will appear at considerably lower levels. Further, not much thought has been given to individual variations in sensitivity.

6.1.2.4.4 Estimations of how much long-term exposure is required to cause the human cortex to reach concentrations of 200 ppm (wet weight)

The calculations refer to a 70 kg "standard man" and a total kidney weight of 300 grams. The cadmium concentration in cortex has been assumed to be 1.5 times the average kidney concentration (section 4.3.2.1).

As has been discussed in section 4.3.4 approximately one-third of the total amount of absorbed cadmium can be estimated to be in the kidneys in a "normal", a man not excessively exposed to cadmium. It is not known exactly what proportion will be in the kidneys in relation to other organs after long-term exposure to cadmium in amounts eventually giving rise to the critical level of 200 ppm (wet weight) cadmium in renal cortex. As was discussed in section 4.3.4, there is no reason to believe that the proportions will differ considerably from what has been estimated for a "normal" man. A decrease to about 25 percent is possible but not probable.

In table 6:2 estimations have been entered on minimum cadmium levels, via ingestion or inhalation, necessary for reaching 200 ppm wet weight in renal cortex after different exposure times and different assumed absorption percentages. The results show, for example, that with 50 years' exposure, a daily intake via the peroral route of about 100-150 μg cadmium with a 5 percent absorption may give rise to renal dysfunction. With a 10 percent absorption, corresponding values would be about 50-75 μg cadmium. Renal dysfunction could be reached via inhalation of cadmium in the ambient air in concentrations of about 1-1.5 $\mu g/m^3$ if a 25 percent absorption is postulated. Corresponding values for a 40 percent absorption would be about 0.5-1.0 $\mu g/m^3$.

The values in table 6:2 refer to cadmium levels in renal cortex which may give rise to renal dysfunction with proteinuria and other effects. Such values of course can not be accepted as "safe" values. In table 6:3 similar calculations have been made but the starting point has been a total body burden of 30 mg cadmium (values of a magnitude reported for "standard American man") corresponding to about 50 ppm (wet weight) in renal cortex. Such a kidney concentration would be reached with a daily peroral intake of about 25-40 μg of cadmium with 50 years' exposure and an assumed absorption of 5 percent. With an absorption of 10 percent the necessary daily intake would amount to about 12-20 μg. For exposure via ambient air a concentration of about 0.25-0.4 $\mu g/m^3$ would suffice, with an assumed absorption of 25 percent of inhaled cadmium. With an absorption of 40 percent concentrations of about 0.12-0.25 $\mu g/m^3$ would constitute a critical level.

Similar tables and calculations, of course, can be made for other alternatives. If one would like, for example, to consider the consequences of lowering the present renal cadmium level in the United States with a factor of 2, the values in the table should be divided by 2.

6.2 EFFECTS ON THE HEMATOPOIETIC SYSTEM AND DOSE-RESPONSE RELATIONSHIPS

6.2.1 Acute effects and dose-response relationships

Effects on the blood after respiratory exposure to high concentrations of cadmium have been noted both in human beings (Beton et al., 1966) and in animals (Prodan, 1932). Beton et al. found elevated levels of hemoglobin in some subjects. This elevation was probably connected with the hemoconcentration caused by the oedema of the lungs. A hemolytic effect after a single injection of cadmium sulphate into a dog (about 25 mg Cd/kg) was noted by Athanasiu and Langlois in 1896, but it is not known if acute respiratory exposure in human beings has ever given rise to such an effect.

It is not possible to establish any dose-response relationships with regard to effects on the hematopoietic system in man or animals after acute exposure. There is a lack of data and the oedema of the lungs and the general toxemia will probably overshadow any other effects.

6.2.2 Chronic effects and dose-response relationships

6.2.2.1 In human beings

Anemia has been described in workers exposed to cadmium oxide dust (Nicaud, Lafitte and Gros, 1942, and Friberg, 1950) and cadmium oxide fumes (Tsuchiya, 1967) but is usually moderate. In a group of 16 workers exposed for 5-30 years to cadmium, a significant correltion was found between high cadmium levels in blood and low hemoglobin levels. (Piscator, unpublished data). The number of white cells is generally normal, but there is an increase in the number of eosinophile cells.in exposed workers (Nicaud, Lafitte and Gros, 1942, Princi, 1947, and Friberg, 1950). No explanation has yet been given .

The bone marrow was examined microscopically by Friberg, 1950, in 19 cadmium exposed workers but no pathological changes were found.

6.2.2.2 In animals

Anemia has been a common finding. Wilson, deEds and Cox, 1941, gave rats food containing 31-500 ppm cadmium and found that the lowest dose gave animals anemia after a couple of months. After exposure had ceased, there was a tendency to normalization in hemoglobin levels. In a group given 125 ppm cadmium for up to 7 months, they noted also increases in reticulocytes and eosinophils. Examination of the bone marrow showed that it was hyperplastic.

Decker et al., 1958, noted that hemoglobin levels had already decreased considerably after 2 weeks in rats given 50 ppm cadmium in drinking water. On the other hand, rats given 10 ppm in water for one year did not become anemic. Friberg, 1950, found that rabbits exposed to cadmium oxide dust developed a slight anemia. A prominent finding was eosinophilia, as 25 percent of the white cells in exposed rabbits were eosinophils compared with 3 percent in a control group. In rabbits injected with cadmium sulphate (0.65 mg Cd/kg), 6 days a week, pronounced anemia was evident after two months of exposure.

In further studies (Friberg, 1955, for exposure conditions, see section 4.2.1.2) it was found that simultaneous administration of iron had a beneficial effect on the anemia, indicating that the anemia was partly due to iron deficiency. By giving ^{59}Fe to cadmium exposed rabbits (1 mg Cd/kg, 6 days a week, subcutaneous injection) , one group receiving the isotope before exposure, another group receiving it after 2 months' exposure, and comparing with controls, Berlin and Friberg, 1960, could show that there was an increased destruction of erythrocytes, even of those formed before exposure. There was no certain difference between controls and exposed animals with regard to utilization of iron for hemoglobin synthesis. The beneficial effect of parenterally given iron also indicated that cadmium did not block hemoglobin synthesis, but that there could be a decreased uptake of iron from the intestines. Berlin and Friberg did not observe any decreased osmotic resistance in the erythrocytes as described by Swensson, 1957. Berlin, Fredricsson and Linge, 1961, found that in rabbits given cadmium there were increased deposits of iron in the bone marrow but no decrease in erythropoietic activity. They found some other changes in the bone marrow, but as the rabbits were rather severely intoxicated after having received subcutaneous injections of 1 mg Cd/kg daily for several months, these changes were regarded as nonspecific and produced by general toxic effects. In a group of rabbits followed after exposure (24 weeks, 0.25 mg Cd/kg, 5 days a week) ceased, hemoglobin levels rose again but were still significantly lower than those in a control group 30 weeks later (Piscator and Axelsson, 1970).

Fox and Fry, 1970, found that ascorbic acid had a beneficial effect on the cadmium produced anemia in Japanese quail. They thought that improved utilization of iron through the action of ascorbic acid was responsible for the beneficial effect.

Berlin and Piscator, 1961, studied blood and plasma volume in cadmium poisoned rabbits and concluded that the anemia could partly be explained as caused by increases in plasma volume. Axelsson and Piscator, 1966b, made long-term experiments on rabbits (for details, see section 4.2.2.2) and found that after 11 weeks of exposure, there was ahaptoglobinemia, indicating hemolysis. They thought at that time that in the chronically exposed rabbit cadmium would be transported to the renal tubules together with hemoglobin released through hemolysis. However, recently, Nordberg, Piscator and Nordberg (unpublished data) have found that cadmium in erythrocytes from exposed mice is stored also in a low molecular weight protein, probably metallothionein,.

6.2.3 Dose-response relationships

The investigations on animals given injections of cadmium have indicated that during exposure anemia will be related to the accumulated dose (Friberg, 1955, Berlin and Friberg, 1960, Berlin and Piscator, 1961 and Axelsson and Piscator, 1966a), but that as soon as exposure has ceased, hemoglobin levels will tend to rise again. When given cadmium in drinking water in concentrations between 0.5 and 10 ppm for one year, groups of rats did not differ from one another with regard to hemoglobin levels (Decker et al., 1958). At these exposure levels, there was thus no dose-response relationship. Hemoglobin levels dropped rapidly, however, in rats given 50 ppm in the water,. The accumulated amount of cadmium could not be related to the anemia since levels in kidneys and liver were higher in rats exposed for one year to 10 ppm in water that in rats given 50 ppm for 3 months.

With regard to human exposure, it is impossible at present to give any statement on dose-response relationships.

6.3 EFFECTS ON THE CARDIOVASCULAR SYSTEM AND DOSE-RESPONSE RELATIONSHIPS

6.3.1 Acute effects and dose-response relationships

Dalhamn and Friberg, 1954, found that an intravenous injection of cadmium sulphate (0.3-0.5 mg Cd/kg) caused a rapid fall in blood pressure within 15 seconds in the cat and the rabbit. Perry and Yunice, 1965, found that an intraarterial injection of 0.1-0.4 mg/kg caused increased diastolic blood pressure in rats, whereas larger doses (0.8-3 mg/kg) caused decreased pressure. Schroeder et al., 1966, found an increase in the systolic pressure after an intraperitoneal injection of 1-2 mg cadmium as cadmium citrate in rats. Hypertension was produced in rats by intravenous injections of cadmium in doses of 0.02-2 mg/kg (Perry et al., 1970) and by intraperitoneal injections of 0.2-2.4 mg/kg (Perry and Erlanger, to be published). The last mentioned authors also found considerable increases in renin activity in blood of rats given an intraperitoneal dose of about 1 mg Cd/kg. The maximum activity was observed 8 hours after injection but a significant increase took place up to one month after injection.

6.3.2 Chronic effects and dose-response relationships

6.3.2.1 In human beings

6.3.2.1.1 In exposed workers

Friberg, 1950, examined 43 workers with a mean exposure time to cadmium oxide dust of 20 years and 15 workers with a mean exposure time of 2 years. The study included physical and roentgenological examination of the heart, electrocardiographic examination at rest and after exercise, and the measurement of blood pressure. No increased prevalence of cardiac disease was found. Electrocardiographic changes occurred to the same extent as in a group of sawmill workers without exposure to cadmium. The majority of the workers had completely normal blood pressures, Nothing supported, an assumption of higher frequency of hypertension in the cadmium workers than that normally expected in workers in relevant age groups. As Friberg did not examine a control group, with regard to the prevalence of hypertension, it is impossible to use his data for a more precise evaluation.

Chest examinations and blood pressure measurements have also been made in other studies (Bonnell, 1955, Bonnell, Kazantzis and King, 1959, Kazantzis et al., 1963, and Holden, 1969) but none of the resulting reports contained findings of cardiac disease or hypertension.caused by cadmium exposure,

6.3.2.1.2 In the general population

Cadmium has been incriminated as one of the factors that may cause hypertension in human beings (Schroeder, 1964, 1965, and 1967). Data by Tipton and Cook, 1963, shows that the cadmium to zinc ratio was higher in people whose deaths were related to hypertension than in other groups. Subjects dying of malignant hypertension with renal failure had low values of both cadmium and zinc in the renal tissues, presumably due to loss of renal tissue. In earlier studies, it had been shown that patients with hypertension excreted more cadmium than did controls (Perry and Schroeder, 1955). These findings, supported by findings in cadmium exposed animals (see next section), initiated epidemiological research.

Carroll, 1966, found a correlation between cadmium concentrations in the air of 28 American cities and death rates from hypertension and arteriosclerotic heart disease. Hickey, Schoff and Clelland, 1967, made a similar study covering 26 cities and found that cadmium together with vanadium was correlated with mortality in heart disease. Hunt et al., 1970, upon reanalysis of Carroll's data, reported a higher correlation between population density and death rates than between cadmium concentrations in air and death rates.

Hunt et al., 1970, made a study of 77 cities in the Middle West of the United States with populations varying between 100,000 and 1,000,000. Cadmium, lead and zinc were measured in the dustfall in residential, commercial and industrial areas from September to December, 1968. Cadmium in milk was also determined in the selected areas. The age-adjusted cardiovascular death rate for 1959-1961 was studied against ten independent variables:

Population density, dustfall, cadmium, lead zinc fallout, total precipitation, average maximum and minimum temperatures and cadmium and lead concentrations in milk. The authors did not find a significant relationship between cadmium fallout and mortality from cardiovascular disease in residential, commercial or industrial areas. There was, however, a significant relationship between mortality and each of the following independent variables: dustfall, lead fallout, and maximum and minimum temperatures, in the residential areas. Minimum temperature was the only variable significantly related to cardiovascular mortality in the commercial and industrial areas.

Pinkerton and Murthy (personal communication) found a significant correlation between cadmium levels in milk and cardiovascular mortality in 58 cities in the United States. Population density was not taken into account, and it is possible that urbanization played a role. Furthermore, the levels reported for cadmium in milk by Pinkerton and Murthy are considerably higher than those stated in other reports (see Chapter 3). As they used the atomic absorption method without extraction of the metal, the possibility that sodium chloride in milk influenced the analysis can not be excluded.

Morgan, 1969, determined renal cadmium in autopsy cases and did not find differences between a group with hypertension and a control group. However, in Czechoslovakia, Lener (personal communication) found that in a group of 12 people (mean age:62) with histories of hypertension, cadmium concentrations in kidney were 36 ppm wet weight, significantly higher than in a control group of 10 people (mean age:59) with a concentration of 27 ppm wet weight. Finally it must be mentioned that according to a report by Nogawa and Kawano, 1969, hypertension has not been found in patients with Itai-itai disease nor in people living near the endemic district where the Itai-itai disease is found in Japan (see section 8.4).

6.3.2.2 In animals

Hypertension has been produced in rats of the Long Evans strain, especially in female rats, by giving them cadmium in drinking water for long periods of time (Schroeder and Vinton, 1962, Schroeder, 1964, and Kanisawa and Schroeder, 1969b). Control rats were given a special cadmium-free diet and the animals to be exposed were given 5 ppm of cadmium (as chloride) in double deionized water together with essential elements, In rats receiving cadmium in drinking water, hypertension usually was manifest after one year. When cadmium was given in hard water (Schroeder, Nason and Balassa, 1967) there was less hypertension. Analysis of cadmium in tissues revealed that cadmium concentrations in the kidneys and liver were of the same magnitude as in American adults, around 40 µg/g and 6 µg/g wet weight, on an average, respectively. (In an earlier investigation of Schroeder and Vinton, 1962, with the same exposure conditions, values of only about one-tenth of these were reported). When the cadmium to zinc ratio was above 0.8, the animals were always hypertensive. Histological examination (Kanisawa and Schroeder, 1969) disclosed renal, arterial, and arteriolar lesions. According to these authors, the changes were indistinguishable from those accompanying benign hypertension from other causes.

Hypertension has also been induced by parenteral injection of cadmium salts. Schroeder et al., 1966, and Schroeder and Buckman, 1967, found that when one or two intraperitoneal injections of cadmium citrate (1-2 mg Cd/kg) were given, hypertension developed and, over a month's period, became equal to the hypertension appearing in rats on which partial constriction of one renal artery had been performed. Similar results are reported by Chiappino and Baroni, 1969, in Spraque-Dawley rats. They also found a hyperplasia of the juxtaglomerular apparatus and of the glomerular zone of the adrenal cortex. They concluded that the renin-aldosterone system probably was stimulated.

Recently Thind et al., 1970, have been able to induce hypertension in rabbits given weekly intraperitoneal injections of cadmium acetate (2 mg/kg) for 7 weeks. During that period mortality was 25 percent. A decrease in vascular responsiveness to angiotensin was suggested as playing a role in the pathogenesis of cadmium hypertension.

Schroeder, Nason and Mitchener, 1968, discontinued exposure to cadmium after 515 days, when rats were hypertensive..They found a lowering of the blood pressure and after 715 days, blood pressure was normal.

The hypertension induced by cadmium could be reversed by giving the chelating agent Cyclohexane-1,2-diamine-NNN'N'-tetraacetic acid (CDTA), which binds cadmium more firmly than zinc (Schroeder and Buckman, 1967). When the disodium zinc chelate was given by intraperitoneal injection to nine rats previously given cadmium in drinking water, blood pressure was normal in all after 2 weeks. However, in rats given cadmium by injections, repeated treatment with the chelate was sometimes necessary to achieve normal blood pressure. After treatment, there was a decrease in cadmium levels in the kidneys and the authors concluded that the lowering of the cadmium to zinc ratio could be the cause of the decrease in blood pressure. For a discussion of the possible toxic effects of cadmium chelates, see section 6.1.1.3).

There are also negative findings in regard to cadmium and hypertension. Lener, 1968, Lener and Bibr, 1970, and Lener (personal communication) reported that hypertension did not appear when Wistar female rats were given cadmium in drinking water (5 ppm) and observed for 16 months. When Long Evans rats were put on 2 percent NaCl for 12 days and then given three intraperitoneal doses of cadmium citrate (1, 1 and 2 mg/kg) with intervals of 1 and 2 weeks, repeated determinations of blood pressure up to 4 weeks after the last injection did not show hypertension. Castenfors and Piscator (unpublished data), using female Sprague-Dawley rats, could not induce hypertension by giving them injections of cadmium chloride (0.5 mg Cd/kg) 3 days a week for 6 months. In another experiment the rats were given cadmium in drinking water (5 ppm) for one year, but monthly determinations of blood pressure did not show any difference compared with controls. At the end of this experiment, the intraarterial blood pressure had a mean value in 13 exposed rats of 153 mm Hg (S.D.: 16) compared with 151 (S.D.: 22) in 9 controls. Lener (personal communication) found that when a group of Long Evans rats were put on 2 percent NaCl for 50 days before receiving 2 doses of cadmium citrate (2 mg Cd/kg) with an interval of 84 days, there was a significant increase in systolic blood pressure in the cadmium exposed animals. Perry, Perry and Purifoy (to be published) produced permanent sodium retention in female rats with 4 injections of cadmium (1 mg/kg) at 1-month intervals. Vander, 1962, had earlier shown that intravenous doses of a cadmium-cysteine complex enhanced sodium reabsorption in the renal tubules. Thus both strain differences and sodium intake might be determining factors in the development of hypertension in experimental animals.

6.3.3 Discussion and conclusions

Since the possibility that cadmium produces cardiovascular disease, especially hypertension, has attracted much interest during recent years, a special discussion on this subject is motivated.

The fact that hypertension has been associated with high kidney levels of cadmium in certain studies can not be used for firm conclusions concerning causality. The data have been obtained by analyses of kidneys from people who died from vascular disease. Nothing has been stated about the previous history or the course of the disease, and the interpretation of the data is subject to the usual difficulties met in this type of epidemiological analysis.

The results from epidemiological investigations are hitherto ambiguous. They have been obtained by associating cardiovascular disease with dustfall data or cadmium concentrations in air. Other, more important sources of cadmium exposure have not been considered. The average cadmium concentration in a "standard American man" seems to be around 30 mg in the age range of 40-50 years (section 4.3.4). Even with such a high average cadmium concentration in the ambient air as 0.01 $\mu g/m^3$, the total amount of cadmium absorbed over a 50-year period would amount to only a small fraction of the total body burden. An absorption rate of inhaled cadmium of 25 percent and a lung ventilation of 20 m^3 /day would thus give a total uptake of less than

1 mg of cadmium over a 50-year period. The cadmium fallout, of course, could influence the cadmium levels of various foodstuffs. It does not seem probable, however, that the average cadmium intake via food by city dwellers in the U.S. is very much dependent upon the local ambient air concentration of cadmium. It was pointed out by Hunt et al. 1970, that population density is a factor of importance. Furthermore, smoking must be taken into account.

In certain areas of Japan where there has been a considerable exposure to cadmium for decades, hypertension has not been associated with cadmium. In addition, there are no reports showing that workers exposed to cadmium have a higher prevalence of hypertension than other groups.

The results from investigations on animals are also ambiguous. It is true that studies show that intraperitoneal injections of cadmium will induce hypertension in rats and rabbits. Long-term exposure via the oral route with relatively low concentrations of cadmium has induced hypertension in rats. There are also negative findings and strain differences as well as other factors might influence the response in rats when cadmium is administered.

Even if thus far the available data do not support a hypothesis that cadmium is causually associated with cardiovascular disease in man, there are reasons to study the question further. The findings, particularly in the animal studies, but even in the epidemiological studies on human beings, merit further attention. Epidemiological studies should be carried out on a longitudinal basis with due consideration given to routes of exposure other than air. Industrial workers with known exposure to cadmium should be included in such studies. More animal experiments should be developed, with particular emphasis upon the mechanisms of cadmium-induced hypertension, as the reasons for the differing results reported by various investigators are not clear.

6.4 EFFECTS ON BONE AND DOSE-RESPONSE RELATIONSHIPS

Cadmium does not accumulate to any considerable extent in osseous tissue, as discussed in section 4.3.2.2. A direct effect of cadmium upon such tissue is therefore unlikely. However, there is evidence that the regulation of the calcium and phosphorus balance by the kidneys can be disturbed by cadmium exposure (see section 6.1.2.1). A disturbed calcium and phosphorus balance can in turn give rise to bone changes but even though the effect upon the calcium balance becomes grave within a very short time, the symptoms and changes in the skeleton require considerable time to develop. Acute effects on bone are not reported and the following account on effects on bone is concerned only with long-term effects.

6.4.1 In human beings

Nicaud, Lafitte and Gros, 1942, described a group of workers exposed to cadmium oxide dust in an accumulator factory. In 2 men (ages: 41 and 60; exposure time: 11 years), 3 married women (ages: 48, 51 and 60; exposure times: 8, 16 and 14 years) and one unmarried woman (age: 37; exposure time: 10 years), there were symptoms of pain in the back and extremities and difficulties in walking. Roentgenological examination disclosed in all 6 workers lines of pseudo-fractures, especially in the shoulder-blades, pelvis. femur and tibia. Proteinuria was not found, but only the boiling test was used. The possibility of tubular proteinuria can not be excluded. Later studies using nitric and trichloracetic acid on other workers in that factory (Friberg, 1950), revealed the presence of proteinuria. Electrophoretic examination of urine from one worker revealed that it was the same type of proteinuria as was seen in the Swedish workers.

Friberg made a roentgenological study of the skeletons of 11 workers from a group of 43 exposed to cadmium oxide dust for 9-34 years (for further details, see section 5.2.1.1) but bone changes were not found. Bonnell, 1955, found at autopsy severe decalcification in a cadmium worker exposed to cadmium oxide fume for 32 years. He died from chronic renal failure. Before his death, proteinuria had been found at repeated examinations. Electrophoretic analysis revealed that this proteinuria was of the type common in chronic cadmium poisoning.

Gervais and Delpech, 1963, found in 8 male workers (ages:49-63; exposure times: 8-30 years) exposed to cadmium oxide fume (7 of them) and cadmium oxide dust (1 of them) the same lines of pseudo-fractures as described by Nicaud, Lafitte and Gros, 1942. These workers had not been exposed for 10-20 years and the symptoms were diagnosed after exposure had ceased. In most cases there was proteinuria which the authors blamed upon lead. Recently, Pujol et al., 1970, have shown that in a worker with bone changes in the same factory, tubular proteinuria and other signs of tubular impairment were present. Adams, Harrison and Scott, 1969, found one case of osteomalacia in a group of workers exposed to cadmium oxide dust. These authors expressed little doubt that this osteomalacia was caused by renal disease since the worker had multiple tubular defects.

Chronic cadmium poisoning in combination with certain dietary deficiencies, i.e. lack of calcium and Vitamin D, seems to be the causative agent for the Itai-itai disease, a bone disease in Japan (see Chapter 8). Of special interest is that the workers in the Swedish factory had a heavy exposure to cadmium oxide dust which gave rise to severe pulmonary and renal changes but not to bone changes (Friberg, 1950). Also the British investigations have not disclosed high incidence of bone disease, except the two above mentioned cases, even though disturbances in calcium and phosphorus metabolism have been common findings (Kazantzis et al., 1963, Adams, Harrison and Scott, 1969). Different nutritional habits will probably play a role. The intake of fat soluble vitamins such as Vitamin D and of calcium is much higher in Sweden and the United Kingdom than in Japan (see Chapter 8, table 8:8). In France, the intake of milk is lower than in Sweden or the United Kingdom. Furthermore, the poor nutritional conditions during the Second World War must have played an important role. It should be pointed out that some French patients and almost all of the Japanese patients have been women and thus more susceptible to calcium and Vitamin D deficiencies.

6.4.2 In animals

Animal experiments have also indicated that exposure to cadmium can cause bone changes. Ceresa, 1945, injected 1 mg $CdSO_4$ daily into rabbits. After two months he observed decreased calcium levels in serum and a decreased mineral content in bone. Maehara, 1968, gave groups of male rats, female rats and ovariectomized rats cadmium in a diet low in calcium (50 ppm Cd for 45 weeks followed by 25 ppm for 5 weeks). He found a decalcification and concluded that this was probably caused by a disturbance of calcium absorption in the digestive tract. He did not report on levels of cadmium in the organs or on proteinuria, so it can not be said to what extent the bone changes were caused by renal dysfunction.

Larsson and Piscator (unpublished data) gave female rats 25 ppm cadmium as the chloride in drinking water. Exposure was for 1 and 2 months and diets with normal and low contents, respectively, of calcium were given. For data after 2 months, see table 4:1. A significant decrease in the mineral content of the bones was found in groups exposed to cadmium and fed a low calcium diet for two months. Cadmium exposure alone and a low calcium diet alone did not cause such a decrease. Furthermore, cadmium levels in liver and kidneys from animals exposed to cadmium and on low calcium diet were 50 percent higher than in animals exposed to cadmium but on a normal intake of calcium, indicating that a low intake of calcium will increase the absorption of cadmium. Studies with injected ^{45}Ca showed that there was the same calcium accretion in the tibia in animals on low calcium and in animals on this diet combined with cadmium exposure. These findings suggested that there was not a direct action of cadmium on bone tissue but that the osteoporosis in cadmium exposed rats on a low calcium diet was caused by an increased bone reabsorption for maintenance of blood calcium.

Zinc has been shown to be important for bone formation. In calves given cadmium orally (350 ppm in the diet for 7 days) the uptake of zinc was increased in most organs but not in bone, in which there was instead a decrease (Powell, Miller and Blackmon, 1967). Lease, 1968, found in the chick that cadmium caused a decrease in the zinc uptake in the tibia.

6.4.3 Discussion and conclusions

A direct action of cadmium upon bone is unlikely, as stated in the introduction to this section. No data has been brought forward to support such a possibility, so it will not be further discussed.

An effect of cadmium upon zinc metabolism, essential for bone tissue, can not be ruled out. Available data, however, do not permit any conclusions as to whether this possible action is critical for bone effects of cadmium.

The effects on bone with all probability are secondary to effects on calcium-phosphorus metabolism. Theoretically, cadmium exposure could influence metabolism of bone minerals in several ways: by affecting the absorption of such minerals in the gastrointestinal tract directly or by influence on Vitamin D activity, by changing the parathyroid activity or by directly affecting the renal regulation of the Ca/P balance.

None of these possibilities has been ruled out entirely by available data. It was shown in section 6.1 that tubular kidney damage and tubular proteinuria are typical features of chronic cadmium poisoning. Increased excretion of bone minerals is not an uncommon cause of kidney stones. An impairment of the renal tubular regulation of Ca/P balance is therefore with all probability the most important factor for elicitation of bone changes in workers with proteinuria. The bone changes reported in the French cadmium workers have features typical of osteomalacia and it is well known that other forms of tubular dysfunction, either hereditary forms or acquired forms can give rise to osteomalacia. Further discussion on the mechanism for elicitation of the so-called Itai-itai disease can be found in Chapter 8.

Concerning the other possibilities for influence on the Ca/P metabolism, the following could be said. The parathyroids regulate blood calcium levels mainly by influencing bone resorption and renal excretion of phosphate and will therefore invariably be involved when disturbances in bone salt metabolism occur. However, at present there is no reason to believe that cadmium influences the parathyroids primarily.

An action on the uptake of calcium from the gastrointestinal tract is most likely of some importance, especially when cadmium exposure is by the oral route. The evidence from the animal experiments by Larsson and Piscator (unpublished data) speaks in favor of such an action. Kidney levels were below those likely to give rise to renal impairment.

The importance of dietary calcium supply for the elicitation of bone changes make precise estimations regarding dose-response relationships impossible. The evidence by Larsson and Piscator, however, showsthat even a relatively short exposure to moderate concentrations of cadmium can influence bone mineralization when the calcium content of the diet is low.

6.5 EFFECTS ON THE LIVER AND DOSE-RESPONSE RELATIONSHIPS

6.5.1 Acute effects and dose-response relationships

An influence on liver function has been recorded in several workers with acute cadmium poisoning after exposure to cadmium oxide fumes (see section 6.1.1). In lethal cases microscopic changes have been noted in the liver and attributed to the general toxemia. These changes have been slight compared to the changes in the lungs.

Prodan, 1932, exposed cats to high concentrations of cadmium oxide fumes for short periods of time and found fatty infiltration in the livers. Similar changes were found in cats exposed to cadmium oxide dust.

Andreuzzi and Odescalchi, 1958, gave rabbits single intravenous injections of doses varying from 1.25-3 mg Cd/kg and determined the GOT-activity in the serum at different times during 72 hours. In the group given 3 mg/kg, the GOT-activity increased considerably after 17 hours, but 60 percent of the animals were dead within 24 hours. When 2.5 mg/kg was given, the GOT-activity increased more than tenfold after 24 hours, but 40 percent of the rabbits died within 48 hours. Rabbits given 2 and 1.25 mg/kg, respectively, survived more than 72 hours. After 24 hours the increase in GOT-activity was about fourfold, but after 72 hours the activity was within the normal range again. These results indicate that a dose near the LD_{50} is necessary in order to induce a severe liver lesion and that the effect on GOT-activity produced by lower doses is reversible.

Kapoor, Agarwala and Kar, 1960, gave rats single subcutaneous injections of 10 mg Cd/kg as chloride, a dose later shown to produce morphologic alterations in rat liver (Favino and Nazari, 1967). The subcellular distribution of cadmium was studied at times varying from 6 to 168 hours after injection. Initially the cadmium concentration was greatest in the nuclear fraction, but later, more was found in the supernatant. Nordberg, Lind and Piscator (to be published) found a considerable decrease in liver weights within the first 6 days in mice given a single subcutaneous injection of 3 mg Cd/kg but no difference in liver weights compared to controls after 18 days.

That acute exposure will give rise to morphological and functional changes in the liver is clear from the foregoing experimental results. In Chapter 4 it was shown that after acute exposure, both via the respiratory tract and via injection, cadmium was accumulated in the liver. It is not known if changes found at autopsy in livers from human beings exposed to high concentrations of cadmium oxide fumes are due to a direct action of cadmium or to the general changes produced by the oedema of the lungs. It is conceivable that cadmium will have a direct action on certain liver functions especially because there is no binding of cadmium to metallothionein during the first hours after injection (see section 4.5). However, the possibility that changes in the cardiovascular system also influence the function of the liver can not be excluded.

6.5.2 Chronic effects and dose-response relationships

6.5.2.1 In human beings

Friberg, 1950, found that the Takata-reaction was positive in 2 and the thymol test in 3 of 19 workers exposed to cadmium oxide dust with a mean exposure time of 20 years. Increases in serum gamma globulin levels were found in several workers. In most other investigations liver function has been little studied, but it will be apparent from the reports of Bonnell, 1955, Kazantzis et al., 1963 and Adams, Harrison and Scott, 1969, that compared to the pronounced changes in renal function, gross changes in liver function are unusual findings in cadmium exposed workers.

6.5.2.2 In animals

Prodan, 1932, found changes in the livers of cats exposed to cadmium via the respiratory or the oral route. Wilson, deEds and Cox, 1941, made similar observations in rats given cadmium orally, 250-500 ppm in the diet for several months. Friberg, 1950, injected cadmium sulphate (0.65 mg Cd/kg) into rabbits six days a week for 2-4 months and found cirrhotic changes. Axelsson and Piscator, 1966a, determined the GOT-activity in serum from rabbits given injections of cadmium chloride (0.25 mg Cd/kg) 5 days a week for 11-29 weeks. They noted that compared with controls, there was no difference after 11 weeks of exposure, whereas there were significant increases in activity after 17 weeks. At that time the concentration of cadmium was around 450 ppm wet weight. Piscator and Axelsson, 1970, made similar determinations in a group of rabbits exposed in the same way for 24 weeks and thereafter followed for another 30 weeks. At that time the GOT-activity was the same in serum from the exposed rabbits and controls. The concentration of cadmium in the liver was about 180 ppm. There was no difference in alkaline phosphatase activity of serum. These findings suggest that the liver damage is reversible.

Long-term studies on effects of cadmium on activities of certain liver enzymes have been performed by Sporn, Dinu and Stoenescu, 1970. In one experiment, rats were given cadmium chloride (1 ppm cadmium) in drinking water for 335 days. An increase in the activity of phosphorylase a and a decrease in the aldolase activity were found, indicating that cadmium may interfere with carbohydrate metabolism in the liver. When rats were given larger amounts of cadmium (10 ppm Cd in food) for shorter periods, an influence of cadmium on the oxidative phosphorylation in the liver mitochondria not seen in the above mentioned long-term experiment was noted.

When zinc was administered simultaneously via the oral route to rats given 10 ppm cadmium in food for 60 days, it was found that whereas zinc prevented the action of cadmium on the oxidative phosphorylation in the mitochondria, it did not prevent changes in the activity of phosphorylase a or aldolase (Sporn et al., 1969).

Cadmium was not determined in organs, so the effect on the enzymes cannot be directly related to liver concentrations. However, Sporn, Dinu and Stoenescu, 1970, estimated that the mean total intake of cadmium in the rats receiving 1 ppm in drinking water for 335 days was 4 mg.

In an experiment by Decker et al., 1958, it was found that animals receiving 0.05 ppm cadmium in drinking water for one year had ingested a total amount of 5.8 mg. In these animals the mean cadmium concentration in the liver was 1.1 ppm. It is conceivable that in the above mentioned experiment by Sporn, Dinu and Stoenescu, 1970, cadmium levels in livers were not much different from the ones reported by Decker et al., 1958. This indicates that cadmium might act upon certain enzyme activities at a liver concentration of the same magnitude as can be found in normal human adults (see figure 4:14).

6.5.2.3 Dose-response relationships

As the liver will accumulate large amounts of cadmium during exposure, functional disturbances could be expected. Liver dysfunction has not been a common finding in exposed workers. The results by Sporn, Dinu and Stoenescu, 1970, indicate that in rats certain liver enzymes may be influenced by cadmium concentrations of the same magnitude as found in normal human adults, but it is not known at present to what extent these findings can be applied to the human liver.

6.6 EFFECTS ON TESTICLES AND DOSE-RESPONSE RELATIONSHIPS

Little attention had been drawn to effects of cadmium on testicles prior to the mid-1950's when Parízek described the destructive effect on testicular tissue (Parízek and Zahor, 1956, and Parízek, 1957). As early as 1919, however, a brief mention was made of a "bluish discoloration of the testicles" of experimental animals in a report on the pharmacology of cadmium (Alsberg and Schwartze, 1919, and Schwartze and Alsberg, 1923), but this information seems to have escaped attention at that time. During the last 15 years, however, a vast literature has been published on different aspects of the destructive action of cadmium on this organ. The following review does not cover all published articles, but gives the more important aspects.

6.6.1 Acute effects in animals

6.6.1.1 Events in cadmium induced testicular necrosis

According to Parízek's description in 1957, a subcutaneous injection of 0.02 mM of cadmium chloride or lactate per kg (2.24 mg Cd/kg) caused macroscopic changes in the testicles within the first few hours after injection. The organs first became swollen and dark red or purple. The weight then decreased rapidly and the testicles became small, hard and yellowish. At the same time the weight of the seminal vesicles and the prostate decreased as a result of a decreased endocrine activity of the testicles. Histologically a capillary stasis and oedema of the interstitium were observed 2-4 hours after injection, followed by extensive hemorrhages according to Parízek and Zahor, 1956. Regressive changes of the seminiferous epithelium were seen 4-6 hours after injection and progressed to a total necrosis within 24-48 hours.

At a certain time (about one month in the rat) after the acute necrosis, a revascularization of testicles (Niemi and Kormano, 1965, and Kormano, 1970) and a regeneration of Leydig cells occurred (Allanson and Deanesly, 1962). Simultaneously, the endocrine activity of the testes returned (Parízek, 1957, Allanson and Deanesly, 1962). When the dose injected was large enough, the germinal epithelium did not regenerate and the testicles thus functioned as endocrine organs only (Kar and Das, 1960, Allanson and Deanesly, 1962 and Gunn, Gould and Anderson, 1963a). About one year after injection, interstitial cell tumors developed (Gunn, Gould and Anderson, 1963a, and Roe et al., 1964; see also Chapter 7).

The sterilizing effect of cadmium is very rapid because simultaneously with the alterations in the testicles, morphologic changes in the spermatozoa of the epididymis and ductus deferens occur. Animals become permanently sterile as early as 24 hours after injection (Kar and Das, 1962a). Cadmium also is extremely toxic for sperm cells in vitro (White, 1955). This sterilizing effect has been studied in a number of animal species both by systemic (see below) and intratesticular (Kar, 1961, 1962, Setty and Kar, 1964, Chatterjee and Kar, 1968, Kar and Kamboj, 1963, and Kar and Das, 1962b) injections.

6.6.1.2 Sensitivity of different animals to testicular necrosis and doses applied

The observations of testicular necrosis by Parízek and Zahor, 1956, and Parízek, 1957, concerned mice and rats. Extensive later studies have confirmed these observations (Meek, 1959, Kar and Das, 1960, Gunn, Gould and Anderson, 1961, 1963a and b, and Allanson and Deanesly, 1962). Similar changes have been shown to occur after systemic administration of cadmium salts to other experimental animals such as rabbits (Parízek, 1960, Cameron and Foster, 1963), monkeys (Girod, 1964a and b), guinea pigs (Parízek, 1960, Johnson, 1969) and golden hamsters (Parízek, 1960) as well as domestic animals, calves (Pate, Johnson and Miller, 1970). However some animal species such as frog, pigeon, rooster, armadilla and opossum (Chiquoine, 1964) and domestic fowl (Erickson and Pincus, 1964, and Johnson, Gomes and Van Demark, 1970) did not develop testicular necrosis, in spite of such doses as 10 and 20 mg $CdCl_2$/kg (corresponding to 6.2 and 12.4 mg Cd/kg) given to the species tested by Chiquoine, 1964. On the basis of these findings, Chiquoine, 1964, suggested that cadmium necrosis is common to species possessing scrotal testes and absent from those possessing abdominal testes. Opossum was an exception to that generalization.

Some strains of mice were also insensitive to subcutaneous injections of 0.02-0.04 mM $CdCl_2$/kg (2.2 -4.4 mg Cd/kg) (Chiquoine and Suntzeff, 1965). Even doses in the lethal range did not produce any testicular effects in some strains of mice, according to experiments performed by Gunn, Gould and Anderson, 1965. They concluded that the amount of cadmium needed to produce minimal testicular damage varied within the susceptible strains. It is of interest in this connection that Lucis and Lucis, 1969, have shown that strains of mice susceptible to cadmium induced testicular necrosis exhibit a greater uptake of cadmium in the testes than strains which are resistant to this action. The lowest subcutaneous dose that has been reported constantly to give rise to testicular necrosis in mice is probably 0.012 mMol/kg (1.34 mg Cd/kg), stated by Gunn, Gould and Anderson, 1968,to be effective for the CD-1 strain.

Gunn, Gould and Anderson, 1965, also tested different doses in different strains of rats. They concluded that the dose of cadmium needed to produce minimal testicular damage differed among various strains and even within the same strains of rats derived from different commercial sources. Usually 0.02- 0.05 mM $CdCl_2$/kg (2.2-5.6 mg Cd/kg) has been used in rats (Parízek, 1957, Kar and Das, 1960, and Gunn, Gould and Anderson, 1961, 1963a and b). In calves intravenous administration of doses as low as 0.20 mg $CdCl_2$ has been reported to give rise to testicular necrosis (Pate, Johnson and Miller 1970).

6.6.1.3 Mode of administration

All the studies mentioned are concerned with acute effects and sequelae of a single injection of cadmium. Subcutaneous, intraperitoneal and intravenous injections of cadmium salts are effective with regard to testicular necrosis in various animal species. Boissou and Fabre, 1965, tested several routes of administration in rats. Large doses (0.25-0.57 mMol/kg, i.e., 28 and 64 mg Cd/kg) administered by the oral route were also reported to give rise to testicular changes similar to those produced by the injection routes. In some large animals, such as calves (Pate, Johnson and Miller, 1970), only the intravenous injection was effective. Kar and Kamboj, 1963, reported that "scrotal inunction" (i.e. painting of $CdCl_2$ solution on the scrotal skin) gave rise to testicular atrophy and sterility in several animal species.

6.6.1.4 Mechanisms for testicular necrosis

The mechanism for development of acute necrosis of the testicles after cadmium injection has been discussed in a number of papers. Parízek, 1957 and 1960, advanced two possibilities for the primary action of cadmium: 1)circulatory failure and 2)action on spermiogenic epithelium. Parízek, 1957, considered the latter possibility more probable. As zinc is essential for the maintenance of germinal epithelium (Elcoate et al., 1955), Parízek considered his own observation (Parizek, 1956) of an antagonistic action of zinc against the necrotizing effect of cadmium supportive of this last mentioned theory. Later Dimow and Knorre, 1967, found changes in the enzymes of the germinal epithelium before histological changes were evident in the testicles. They considered their results to be in favor of a direct action of cadmium on germinal epithelium. Hodgen, Gomes and

Van De Mark, 1970, have detected an isoenzyme of carbonic anhydrase in rat testis not found in rat kidneys or erythrocytes. They suggested that this organ specific carbonic anhydrase was the primary site of action of cadmium in the testicle. Hodgen and his colleagues (Hodgen, Butler and Gomes, 1969, and Hodgen, Gomes and Van De Mark, 1970) also showed that the activity of this isoenzyme decreased already 30 minutes after cadmium injection and later ceased entirely. Hodgen, Gomes and Van De Mark, 1969, showed that the testicular isoenzyme was found in both rat testicular artery and testicular parenchyma. Thus these studies did not reveal whether the action of cadmium took place in the interstitium or in the tubules of the testicle.

Whatever may be the molecular basis for the cadmium action, it has been well established that the vascular bed and the blood flow of the testicles are affected very early after injection of cadmium. This has been shown with histological (Kar and Das, 1960 and Gunn, Gould and Anderson, 1963b), electron microscopical (Chiquoine, 1964 and Clegg and Carr, 1967), angiographic (Niemi and Kormano, 1965), and functional (Waites and Setchell, 1966, Clegg and Carr, 1967, Carr and Niemi, 1966, Johnson, 1969 and Setchell and Waites, 1970) techniques. Because the injected cadmium is concentrated in the interstitial tissue (Berlin and Ullberg, 1963, and Nordberg, unpublished data), and never reaches the germinal epithelium in any detectable amounts, the changes observed in this epithelium most probably are secondary to the vascular damage.

6.6.1.5 Protective measures

The necrotizing action of cadmium can be prevented by specific treatments. The effectiveness of the administration of zinc in this respect has already been mentioned. Totally 80-200 times the molar equivalent of zinc acetate given in three injections: 5 hours before, simultaneously with and 19 hours after the cadmium afforded complete protection of the testicles of the rat against 0.04 mMol of Cd/kg (Parízek, 1956, 1957 and 1960). These observations have been confirmed by other investigators (Gunn, Gould and Anderson, 1961) who used a total of 3 mMol/kg of zinc to prevent testicular damage from 0.03 mMol Cd/kg in Wistar rats. It was also shown that the duration of the prevention made possible by zinc was dependent upon the breeding of the animals. Animals bred immediately after injection of Cd + Zn showed a sharp decrease in fertility 4 weeks later, whereas animals bred 8 weeks after injection were still fertile 12 weeks after injection.

Selenium (0.04 mMol/kg) also protects the rat testicles against the necrotizing action of cadmium (0.02 mMol/kg) as shown by Kar and Das, 1963. The same effect of selenium was studied in the mouse by Gunn, Gould and Anderson, 1968b. The last mentioned authors also showed in an earlier communication (Gunn, Gould and Anderson, 1966) that thiols such as cysteine and dimercaptopropanol (BAL) prevented cadmium induced necrosis in the testicles. Cobaltous chloride given to rats in a dose of 30 mg $CoCl_2$/kg 17 hours prior to administration of 6.60 mg cadmium chloride/kg also protected the testicles from damage (Gabbiani, Baic and Déziel, 1967).

Ito and Sawauchi, 1966, reported that injection of 1/2 to 1/4 of a testis destructive dose of cadmium chloride (0.1 ml of a 0.1% $CdCl_2$ solution per mouse) 2 days prior to the injection of the normally testes destructive dose prevented testicle destruction in more than half of the animals. This protective effect of pretreatment with the harmful agent itself has later been confirmed in our own laboratory (Nordberg, unpublished observation).

6.6.2 Chronic effects

6.6.2.1 In animals

From the point of view of environmental exposure, acute effects of large doses are of limited interest. Histological changes in the testicles of rats as a result of long-term administration of cadmium in the food were reported by Pindborg, 1950 and Ribelin, 1963. Pindborg gave doses of 0.025-0.1 percent $CdCl_2$ (= 150-610 ppm Cd) and Ribelin, 50-1270 ppm cadmium in the diet. The changes reported by Ribelin were different from those developing after a single injection but were not different from those produced by several other toxic substances tested by Ribelin. On the whole it is difficult to judge the frequency of the changes from the paper published by Ribelin as no data are given concerning number of animals, frequency of testicular alterations or the appearance of toxic reactions in other organs. In a brief report by Richardson and Fox, 1970, testiclar development was studied in Japanese quail which had received 75 ppm Cd in the diet up to 4 weeks of age. Seminiferous tubules lined with undifferentiated cells were said to have occurred in more than half of the tubules. Though it is impossible to judge the nature of the testicular damage from the short communication, it seems that no total testicular necrosis occurred.

Piscator and Axelsson, 1970, reported on histological and electron microscopic examinations of testicles from rabbits exposed by repeated daily subcutaneous injections of cadmium for as long as 24 weeks and followed for another 30 weeks before killed. The investigators did not observe any pathological changes in the testicles, in spite of the presence of kidney damage. They stated that the absence of testicular changes could be explained either by rabbits' comparative insensitivity to the necrotizing action of cadmium or by the protection of the testicles by metallothionein formed in the liver. In order to shed some light on this question, Nordberg (unpublished data) performed studies on mice of the CBA strain which is very sensitive to cadmium induced testicular necrosis. By repeated injections considerable amounts of cadmium were accumulated in the organs including the testicles but no histologically evident changes were found in this organ. These data evidently were in favor of the second alternative suggesting a protective effect of metallothionein against the necrotizing action on the testicles. Such a metal binding protein was also found in the livers of the CBA mouse (Nordberg, Piscator and Lind, to be published). Injection of cadmium bound to metallothionein did not produce any testicular necrosis in doses effective in this respect when injected alone (Nordberg, unpublished data). The earlier mentioned observations by Ito and Sawauchi, 1966, of a protective action of small doses of cadmium are consistent with the finding that no testicular necrosis has occurred in animals exposed repeatedly to cadmium.

Another observation which might be relevant when discussing long-term effects on the testicles is the decrease in proteinuria demonstrated in mice repeatedly injected with $CdCl_2$ for several months (Nordberg and Piscator, unpublished data). Male mice normally excrete a high concentration of protein in the urine. The major urinary protein is synthesized in the liver under the influence of testosterone (Finlayson and Asofsky, 1965, Roy and Neuhaus, 1966 and Roy, Neuhaus and Harmison, 1966). The observed decrease in proteinuria during cadmium exposure might therefore be a result of an action of cadmium on the production of testosterone in the interstitial cells of the testicles. The observation that cadmium accumulates in the interstitial tissue (around the capillaries) of the testicle (Nordberg, unpublished data) favors such a possibility.

6.6.2.2 In human beings

The reports of acute testicular necrosis after systemic administration of cadmium salts in a great number of animal species strongly suggests that a similar effect is likely in human beings. However, such testicular necrosis has not been reported to be a result of cadmium exposure. Smith, Smith and McCall, 1960, found high values of cadmium in the testicles of men industrially exposed to cadmium fume. These authors also reported some histological changes in the testicles at post mortem examination. The changes were of a rather unspecific nature, however, and the authors therefore ascribed them to the terminal illness. It is difficult, however, to exclude the possibility that these histological changes had some association with the cadmium exposure. Favino et al., 1968, investigated the fertility of 10 cadmium workers and also analyzed androgens in blood. In this investigation one case of "impotency" with abnormally low testosterone levels in the blood was found. Further studies similar to those made by Favino et al. are necessary before any conclusion can be drawn concerning the possible effect of cadmium on the endocrine function of the testicles of people exposed to cadmium.

6.6.3 Dose-response relationships

The lowest dose effective for elicitation of acute testicular changes in calves is 0.2 mg $CdCl_2$/kg(0.12 mg Cd/kg) given by the intravenous route (Pate, Johnson and Miller 1970).A subcutaneous injection of cadmium salts in a dose of 0.01 mMol/kg (1.1 mg/kg) can produce a total testicular necrosis in some animals (e.g. certain strains of mice). For other animals (e.g. rabbits) higher doses are required. Some animal species or certain strains of a species are so resistant to the acute necrotizing action of cadmium, that even doses in the lethal range do not cause alterations. The dose-interval between no-effect and total testicular necrosis is very narrow for a given kind of animal. Testicular necrosis can be prevented by zinc, selenium, cobalt, thiol compounds or pretreatment with a smaller dose of cadmium.

All data on testicular necrosis are from animal experiments. As many mammalian animal species including monkeys are susceptible to the action of cadmium on the testicles, it is highly probable that a similar effect would occur also in human beings. However, as cadmium is not used as a drug, people can not be exposed by injections. If the absorbed dose necessary for elicitation of testicular changes is proportionally the same as the lowest subcutaneous dose in animals (1 mg Cd/kg), this means that 70 mg should be absorbed in a short time in a 70 kg man, an unrealistic exposure.

For chronic exposure no conclusive data are available concerning effects on the testicles. Animal experiments suggest that there might be a possibility for effects of a somewhat different nature from those seen after a single injection. As yet, no evidence on human exposure has proven an effect on the testicles. Accordingly no dose-response relationships for chronic exposure can be discussed.

6.7 OTHER EFFECTS

6.7.1 In human beings

During the years many different symptoms have been reported in men exposed to cadmium. These include loss of appetite, loss of weight, fatigue, increases in the E.S.R. etc. These unspecific symptoms can be related to the systemic effects. More specific effects have been a yellow coloring on the proximal part of the front teeth (Barthelemy and Moline, 1946, and Friberg,

1950) and anosmia (Friberg, 1950). The last mentioned effect was found in about one-third of a group of workers with a mean exposure of 20 years to cadmium oxide dust. That anosmia is common in workers exposed for long periods of time to cadmium oxide dust was also noted by Baader, 1951. Suzuki, Suzuki and Ashizawa, 1965, and Tsuchiya, 1967, did not find an increased prevalence of anosmia in workers exposed to cadmium stearate and cadmium oxide fumes, respectively.

Pancreatic function has attracted very little interest, which is regrettable as the high concentrations of cadmium in the pancreas found at autopsy of cadmium workers(section 4.3.2) have indicated the possibility of a disturbed function. According to Murata et al., 1970, a decrease in pancreatic function is a feature of the Itai-itai disease.

Gastrointestinal effects have been a common findings in earlier reports on acute cadmium poisoning due to ingestion of food highly contaminated with cadmium. The contamination was usually caused by storage of food in cadmium plated containers, cans, etc. Nausea, vomiting, abdominal pains and diarrhea have been reported symptoms (Lufkin and Hodges, 1944, Cole and Bauer, 1944, Report from United States Public Health Service, 1942). Even if the outbreaks of food poisoning due to cadmium have decreased considerably since cadmium has been prohibited in utensils for cooking and storing food after the Second World War, some reports during the later years indicate that this problem might still exist (Rèine and Peres, 1959, and Baker and Hafner, 1961). The prognosis seems good but there have been no reports on detailed follow-ups.

Symptoms from the nervous system have been reported by Vorobjeva, 1957, who investigated 160 workers in an accumulator factory. Subjective symptoms consisted of headache, vertigo, sleep disturbances etc. Physical examination revealed increases in knee-joint reflexes, tremor, dermographia and sweating. Special investigations on sensory, dermal, optic and motoric chronaxia showed that the cadmium exposed workers with subjective disturbances also had changes on these tests.

Cvetkova, 1970, studied 106 women (ages: 18-48) employed in cadmium industries. Sixty-one worked in an alkaline accumulator factory, 21 in a zinc smelter and 24 in a chemical factory. A control group consisted of 20 women. Levels of cadmium in air varied between 0.1-25, 0.02-25 and 0.16-35 mg/m^3, respectively. Exposure times were not given in the report. In the alkaline accumulator factory and the zinc smelter groups, the weights of newborn children, 27 in each group, both boys and girls, were significantly lower than the weights of children born to members of the control group. In 4 of the 27 children born to women in the zinc smelter group, signs of rachitis and delayed development of teeth were recorded. The author concluded that pregnant women should not work in a cadmium contaminated environment.

Large doses of cadmium are toxic to nervous ganglia, as has been shown by Gabbiani, 1966, who gave rats subcutaneous injections of cadmium chloride (2.5-28 mg Cd/kg) and found severe hemorrhagic ganglionic lesions. Gabbiani, Baic and Déziel, 1966, found that by giving rats as pretreatment 5 subcutaneous injections of cadmium chloride in a relatively small dose, (2mg/kg), the ganglionic lesions produced by a single intravenous dose of 8 mg/kg were prevented. Damage to the cerebrum and cerebellum was found in newborn rats and rabbits receiving cadmium (Gabbiani, Baic and Déziel, 1967), whereas in mature animals, such changes were not found. Gabbiani, Gregory and Baic, 1967, found that pretreatment with zinc acetate prevented the development of ganglionic damage.

There have not been any long-term experiments in which small doses of cadmium were administered in order to investigate nervous functions.

Cvetkova, 1970, exposed female rats via the respiratory route to cadmium sulphate (about 3 mg/m^3) during pregnancy. On the 22nd day, half of the group was killed and the embryos were taken out. There was the same number of embryos in exposed rats as in a control group, but the mean weight was lower in the exposed group. Analysis of liver from embryos showed a higher content of cadmium in the exposed group. In the exposed group in which pregnancies were allowed to be full-term, the weight of the newborns was lower than in controls. After 8 month , the weights in the exposed group were still lower. The rats born to the exposed group also had an increased mortality during the first 10 days after birth.

¶With regard to influence on endocrine glands it has been shown that a single subcutaneous injection of cadmium chloride (10 mg/ Cd/kg) given to male rats causes a prompt decline in pituitary FSH level and an increase in LH (Kar, Dasgupta and Das, 1960). These changes were thought to be caused by the testicular damage and it is not known if cadmium exerts a direct effect upon the pituitary. In this connection, it is of interest that Berlin and Ullberg, 1963,noted an uptake in the pituitary gland after a single dose of radioactive cadmium. Influence on the thyroid has been demonstrated by Anbar and Inbar, 1964, who gave mice (weight not given) 0.12 mg Cd by the intraperitoneal route. They found a decrease in the uptake of iodine, but as the dose was large and other metals, both essential and non-essential had the same effects, no certain conclusions can be drawn from the experiment. A decrease in the uptake of iodine was also found by Balkrishna, 1962, who gave rats single intramuscular injections of cadmium chloride (10 mg Cd/kg).

Baum and Worthern, 1967, found amyloid deposits in the glomeruli of rabbits given intramuscular injections of cadmium chloride, 1 mg Cd/kg, a total of 68 injections in 22 weeks, or the same dose for 9 weeks, a total of 47 injections. Similar findings have also been described by Vigliani, 1969, in rabbits exposed for 7-13 months to cadmium (0.25 mg Cd/kg subcutaneously,5 days a week). He attributed the amyloid deposits to disturbances in immunglobulin metabolism.

6.8 CONCLUSIONS

Acute manifestations in animals have been studied mainly by injection of cadmium. It has been possible to show effects from most organ systems, including hypertension, testicular, liver and renal damage. Doses have varied between 1-20 mg cadmium/kg. The results show that cadmium is an extremely toxic metal but they have only limited bearings on the effects produced by long-term exposure to cadmium.

In human beings acute poisonings with local symptoms from the gastrointestinal tract are known to have occurred due to ingestion of cadmium contaminated food or beverages. Systemic effects, however, are not known.

Long-term exposure gives rise to renal tubular damage in animals. Workers with prolonged exposure to cadmium oxide dust or cadmium oxide fumes will develop renal tubular dysfunction. A characteristic sign of the renal dysfunction is proteinuria of the so-called tubular type. This is considered to be due to a decreased tubular reabsorption of filtered proteins. Cadmium seems to be transported to the kidney with a low molecular weight protein, metallothionein. The reabsorption of this protein will also decrease and the result will be an increased excretion of cadmium. Other signs of the renal tubular dysfunction, usually appearing after the proteinuria, are glucosuria and amino-aciduria and changes in the metabolism of calcium and phosphorus.

Evidence from animal experiments and from analyses of cadmium in kidneys from workers exposed to cadmium indicates that renal dysfunction may become manifest at levels around 200 ppm wet weight in renal cortex. A daily peroral intake of about 100-150 µg cadmium may result in a reaching of this level after 50 years of exposure with an absorption of 5 percent. Based on an absorption of 25 percent of inhaled cadmium, concentrations of cadmium in ambient air of about 1-1.5 µg/m^3 will give the same results. In a factory, the necessary concentration during 25 years of exposure would be about 8 µg/m^3. In these estimations, simultaneous exposure via food has not been taken into account. In table 6:2, the exposures required to reach the critical level in the kidney are given together with other assumptions concerning absorption.

Osteomalacia has been observed in workers industrially exposed to cadmium. It is considered to be mainly due to a disturbance in calcium and phosphorus metabolism caused by the renal tubular dysfunction.

There is evidence that hypertension can be induced in animals either by single injections or by repeated exposure to cadmium in drinking water. In human beings who have died after a history of hypertensive disease, cadmium levels in kidneys have been higher than in people who have died from other diseases. The cause of the association found is not clear. Epidemiological investigations have indicated a relationship between cadmium levels in air and cardiovascular disease. There is reason to believe that this association is spurious and in any case, no causal association has been proven.

Other long-term effects that have been noted are anemia and liver dysfunction, as shown in both animal experiments and investigations on exposed workers. Animal data have indicated that the activities of enzymes engaged in carbohydrate metabolism might be changed at concentrations of cadmium in liver within the range found in livers of normal human beings. The significance of this finding for man is not known.

Testicular changes have been noted during long-term exposure. These changes are milder than the pronounced testicular damage caused by acute doses of cadmium. It is not known if the testicles will be affected in man during long-term exposure.

Table 6:1 CONCENTRATIONS OF CADMIUM IN KIDNEY CORTEX (ppm wet weight) IN WORKERS EXPOSED TO CADMIUM OXIDE DUST IN RELATION TO MORPHOLOGICAL KIDNEY CHANGES SEEN AT AUTOPSY OR BIOPSY.

Worker	Morphological changes	Proteinuria	Cadmium in cortex §)	Age	Years exposed	Years since last expos.	Years of autopsy(A) or biopsy(B)	References
S.W.H.	++	+	83	46	28	1	1950(A)	Kazantzis et al., 1963.
K.J.	++	+	75	49	22	9	1951(A)	Friberg, 1950, 1952 and 1957.
K.N.	§§)	+	20	57	18	6	1952(A)	Friberg, 1950 and 1957.
H.B.	++	+	33	60	26	3	1949(A)	Friberg, 1950 and 1957.
A.B.	++	+	174		16	4	1950(A)	Baader, 1951, Hörstebrock, 1951
O.J.	++	+	63	62	20	1	1967(A)	Piscator, unpublished data.
G.J.	(+)	+	321	44	11	12	1959(B)	Axelsson and Piscator, unpublished data.
G.K.	(+)	+	152	46	15	0	1959(B)	"
A.L.	-	(+)	220	36	6	0	1959(B)	"
E.Y.	-	-	446	39	7	0	1959(B)	"
E.H.	-	+	320	40	15	10	1959(B)	"
J.P.	-	+	330	43	20	6	1959(B)	"
N.U.	-	-	180	44	12	0	1959(B)	"
H.N.	-	+	21	45	13	0	1959(B)	"
K.N.	-	-	190	50	15	2	1959(B)	"

§) Underlined figures are based on cadmium concentrations in whole kidney, assuming that the cadmium concentration in cortex is 1.5 times the average kidney concentration (section 4.3.2.1.)

§§) Results from histological examinations not reported but at examination in 1946 (Friberg, 1950) this worker had the lowest kidney function tests of all (Inuline clearance: 42ml/min; Concentration capacity: 1.016; NPN: 44 mg %.

Table 6:2 ESTIMATED MINIMUM CADMIUM LEVELS VIA INHALATION ($\mu g/m^3$) OR INGESTION (total daily intake) NECESSARY FOR REACHING 200 ppm (wet weight) OF CADMIUM IN RENAL CORTEX (total body burden: 120 mg cadmium) AFTER DIFFERENT EXPOSURE TIMES AND FOR DIFFERENT ABSORPTION RATES OF CADMIUM.x)

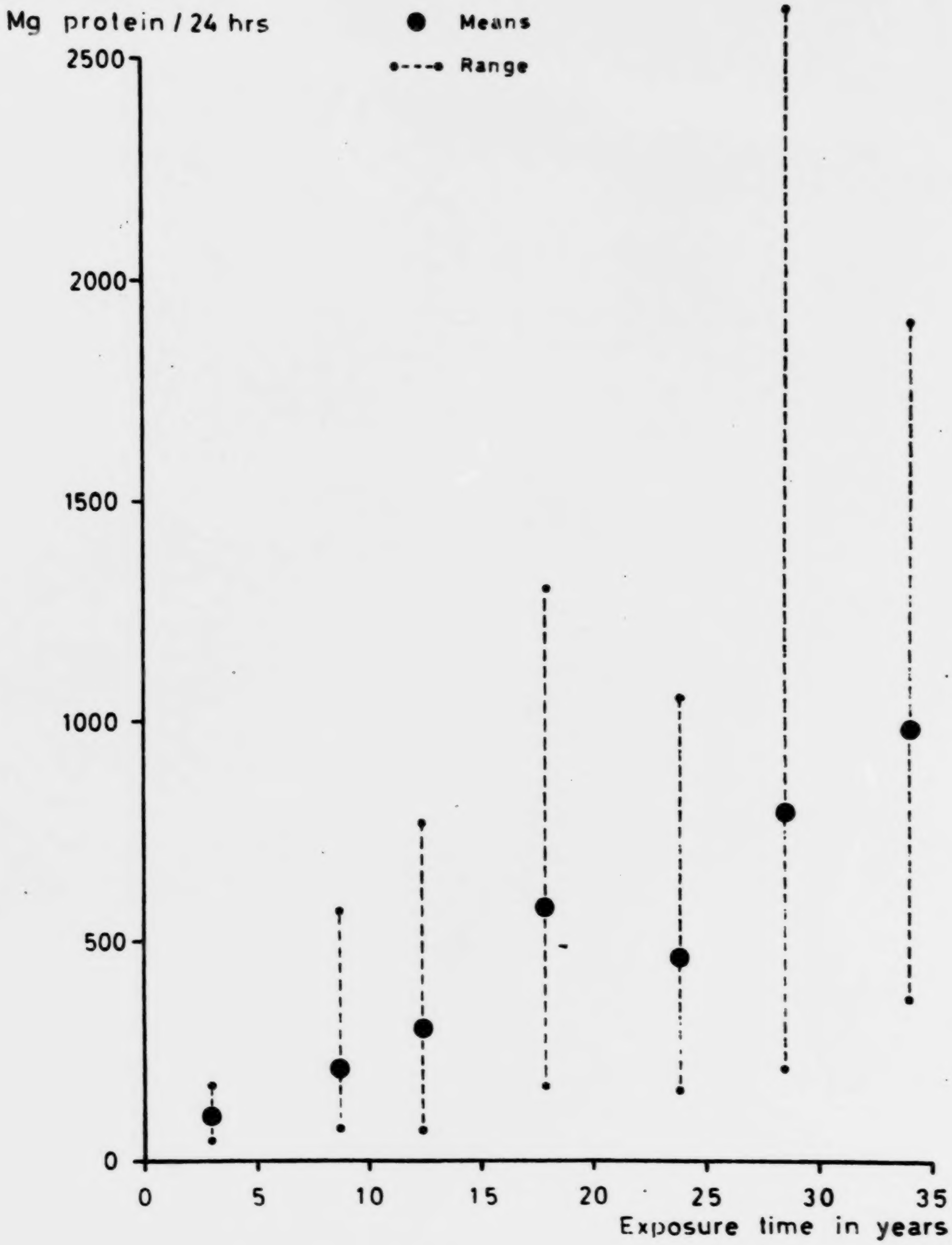
Years of exposure	Ingestion total daily intake, μg Cd			Ambient air μg Cd/m^3			Industrial air μg Cd/m^3		
	absorption percent			absorption percent			absorption percent		
	2.5	5	10	10	25	40	10	25	40
10	1324	662	331	16.2	6.5	4.1	52.5	21	13.1
25	530	265	132	6.5	2.6	1.6	21.0	8.4	5.2
50	265	132	66	3.2	1.3	0.8	10.5	4.2	2.6

x) A lung ventilation of 20 m^3 per day has been used for evaluation of ambient air exposure. A lung ventilation of 10 m^3 per 8 hours 225 days per year has been used for evaluation of industrial air exposure. In no case have the cumulative effects of different types of exposure been taken into account. The results have not been corrected for excretion, as it has been considered insignificant.

Table 6:3 ESTIMATED MINIMUM CADMIUM LEVELS VIA INHALATION (µg/m^3) OR INGESTION (total daily intake) NECESSARY FOR REACHING 50 ppm (wet weight) OF CADMIUM IN RENAL CORTEX (total body burden: 30 mg) AFTER DIFFERENT EXPOSURE TIMES AND FOR DIFFERENT ABSORPTION RATES OF CADMIUM.[x)]

Years of exposure	Ingestion total daily intake, µg Cd			Ambient air µg Cd/m^3			Industrial air µg Cd/m^3		
	absorption percent			absorption percent			absorption percent		
	2.5	5	10	10	25	40	10	25	40
10	331	166	83	4.0	1.6	1.0	13.0	5.1	3.3
25	132	66	33	1.6	0.7	0.4	5.1	2.1	1.3
50	66	33	17	0.8	0.3	0.2	2.6	1.1	0.7

[x)] A lung ventilation of 20 m^3 per day has been used for evaluation of ambient air exposure. A lung ventilation of 10 m^3 per 8 hours 225 days per year has been used for evaluation of industrial air exposure. In no case have the cumulative effects of different types of exposure been taken into account. The results have not been corrected for excretion, as it has been considered insignificant.



The values were obtained about 10 years after the last exposure.

Figure 6:1 Relation Between Exposure Time and Protein Excretion for 40 Cadmium Workers Divided into 5-Year Exposure Groups (from Piscator, 1966c).

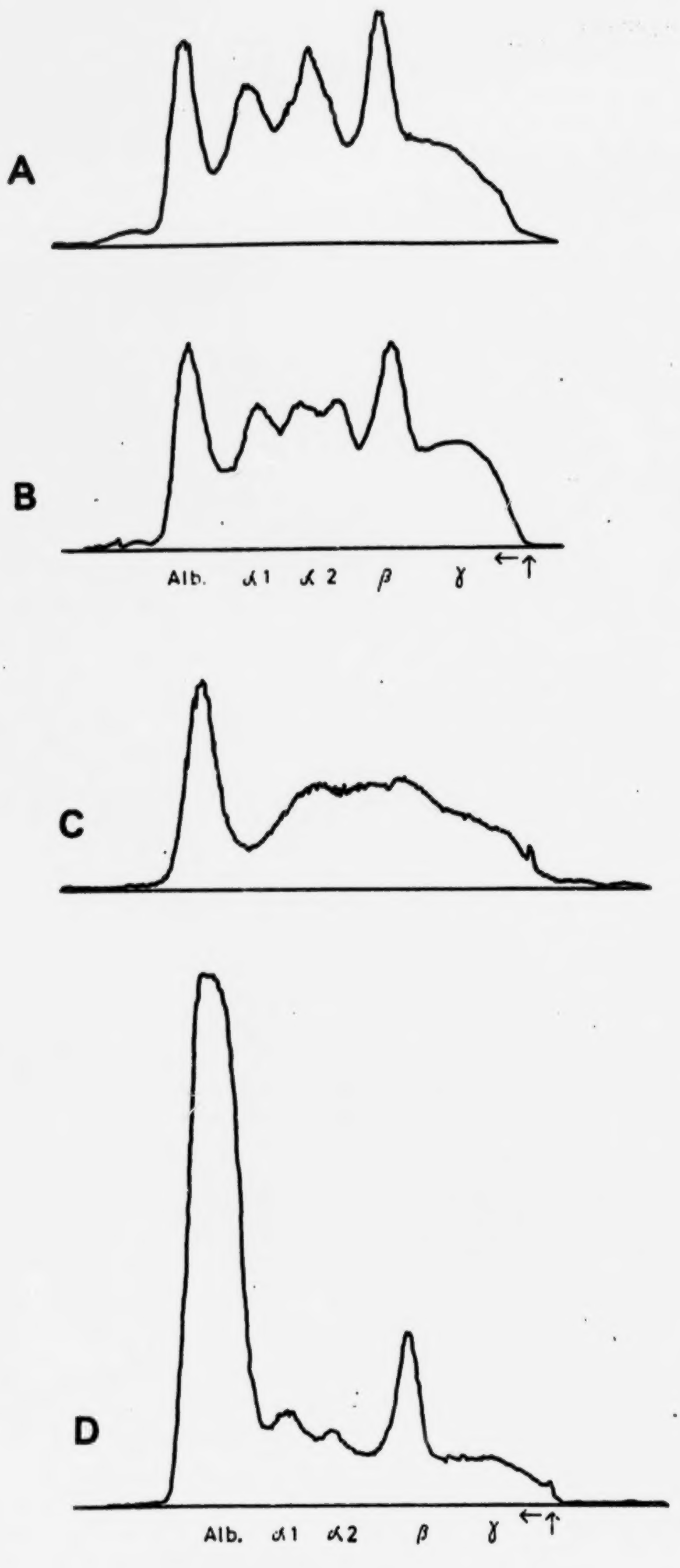


Figure 6:2 Scanned Electrophoretic Patterns for Urinary Proteins A and B). Cadmium Workers C). Normal man D). Person with Chronic Nephritis (from Piscator, 1966c).

CHAPTER 7

CARCINOGENIC AND GENETIC EFFECTS

7.1 CARCINOGENIC EFFECTS

Information in regard to a possible carcinogenic effect of cadmium and cadmium compounds is given primarily from animal experiments. Only a very few reports dealing with such effects in human beings have appeared.

7.1.1 In animals

In 1961 Haddow, Dukes and Mitchley reported that repeated subcutaneous injections of rat ferritin produced sarcoma at the site of injection in rats. Testicular atrophy and benign Leydig cell tumors were also seen. The ferritin contained considerable amounts of cadmium because it had been prepared from rat-liver protein by precipitation with a cadmium salt. The findings prompted further studies using cadmium alone and different investigators showed that cadmium and cadmium compounds injected subcutaneously or intramuscularly in rats could induce sarcoma. In 1964 Haddow et al. induced sarcoma at the site of subcutaneous injection with cadmium sulphate in 14 out of 20 rats but observed no tumors in mice after similar injections. In the same study, Roe et al., 1964, found testicular atrophy and Leydig cell hyperplasia and neoplasia. Gunn, Gould and Anderson, 1963a and 1964, induced interstitial cell tumors in the testes of rats as well as subcutaneous sarcoma with a single subcutaneous injection of cadmium chloride. Both forms of cadmium-induced tumors were inhibited by subcutaneous administration of zinc acetate. Later, the same authors (Gunn, Gould and Anderson, 1967) showed that a single subcutaneous or intramuscular injection of cadmium chloride in concentrations as low as 0.17 to 0.34 mg of cadmium induced sarcoma. No tumors arose in skin, liver, salivary glands, prostate or kidney. The authors concluded that cadmium may be one of the most potent metallic carcinogens yet known.

Kazantzis, 1963, and Kazantzis and Hanbury, 1966, showed that sarcomata could also occur after injection of a single dose of cadmium sulphide. Metastatic tumors were seen in regional lymph nodes and lungs. Heath et al., 1962, showed that cadmium given as a metal powder intramuscularly to rats induced sarcomata. Such tumors could be maintained by transplantation. At the time of publication, the cadmium tumors had been maintained for 6 years and 75 transplants (Heath and Webb, 1967). Most of the inducing metal was incorporated intracellularly by the primary tumors and bound by the nuclear fraction. Smaller amounts were found in the mitochondrial and soluble fractions.

Schroeder and collaborators (Schroeder, Balassa and Vinton, 1964 and 1965, and Kanisawa and Schroeder, 1969) reported on life-term studies on the effect of trace elements on tumors in rats and mice. The rats given cadmium had more tumors than their controls while the opposite was true for mice. Schroeder concluded that the oral ingestion of cadmium can not be considered carcinogenic in the doses given.

7.1.2 In human beings

Potts in 1965 reported on the prevalence of cancer among workers exposed to cadmium oxide dust in the production of alkaline batteries. Among 74 men with at least 10 years' exposure to cadmium, 8 had died, 3 of them from cancer of the prostate and 2 from other forms of cancer. That the workers had been exposed to toxic amounts of cadmium was obvious from the high prevalence of proteinuria and anosmia. Potts did not examine any control group and did not draw any firm conclusions. He recommended as a matter of urgency, however, that the possibility of some association between cancer in man and cadmium as used in industry must be fully explored.

Kipling and Waterhouse, 1967, briefly mentioned the incidence of cancer in a group of 248 workers exposed for a minimum of one year to cadmium oxide. The type of work was not stated. From annual incidence rates supplied by the Birmingham regional cancer registry, it was possible to compute expected values and to compare with observed values. For cancer of the prostate, 4 cases were observed versus an expected number of 0.58.

Out of the 58 male workers in an alkaline battery plant examined by Friberg, 1950, (see sections 4.3.1 and 5.2.1.1.1) 15 had died in 1970 (Friberg, unpublished data). The cause of death in three cases was cancer (urinary bladder, primary pulmonary and large bowel, respectively). No control groups have been studied and no conclusions have been drawn as yet.

Humperdinck, 1968, reported on a follow-up of 8 cases of chronic cadmium poisoning described by Baader in 1951. Four deaths had occurred, one due to primary cancer of the lung. Out of all workers (536) who during 1949 to 1966 had had any contact with cadmium, 5 had contracted carcinoma (including the above mentioned case of lung cancer). The author concluded that the data did not support any causal relationship between cadmium exposure and cancer. It should be added, though, that the majority of the workers were relatively young with relatively short periods of contact with cadmium (269 for less than one year, only 4 for 7-11 years). The study, thus, does not elucidate the question of a possible association between cadmium exposure and cancer. It should be of value to study the group on a longitudinal basis, particularly if more detailed information on exposure levels can be made available.

Holden, 1969, very briefly reported one case of carcinoma of the prostate and one of the bronchus among 42 men exposed to cadmium fumes from 2 to 40 years.

Winkelstein and Kantor, 1969, reporting data from the Erie County and the Nashville Air Pollution Studies, found an association between prostatic cancer and concentrations of suspended particulate air pollutants in both studies. The authors were cautious in view of the small numbers but drew attention to earlier reports of an association between cadmium exposure and cancer of the prostate.

Morgan, 1969, studied the renal and hepatic cadmium levels for different disease groups at autopsies. In cancer patients she found such a wide variation in concentrations of cadmium that a further study was warranted. In two later investigations she pursued similar studies of bronchogenic carcinoma and emphysema. Cadmium was analyzed by atomic absorption spectroscopy with good recovery and repeatability. In the first of these two further investigations (Morgan, 1970) she compared the cadmium concentrations in a group of male patients who had died from bronchogenic carcinoma with a control group and with a group who had died from other forms of neoplasia. The results are shown in table 7:1. The average cadmium concentrations in the group who had died of bronchogenic carcinoma were statistically higher than those in the other groups.

In the second of the later investigations Morgan (unpublished data) reexamined her material and compared the controls with 3 groups: one group of patients with bronchogenic carcinoma with emphysema, one group with bronchogenic carcinoma without emphysema, and one group with only emphysema. The purpose was to examine whether both emphysema and bronchogenic carcinoma were associated with high cadmium levels. She found that "renal cadmium content was elevated in both groups with cancer. Hepatic cadmium was increased in both emphysema alone and in combination with lung cancer as well as lung cancer alone." In 36 controls, the average value for the liver (μg/g ash) was 170 (S.D.: 95) against 290 (S.D.: 155) in the group with only emphysema. Corresponding values for the kidney were 2512 (S.D.: 1427) and 2921 (S.D.: 1252).

Morgan interpreted her findings with great caution. She pointed for example to earlier observations (Olson et al., 1954, and Teitz, Hirsch and Neyman, 1957), in which tissue trace metal concentrations were found to be abnormal in a wide variety of neoplastic diseases. Furthermore, she added that there is no convincing evidence that bronchogenic carcinoma has been associated with industrial exposure to cadmium. Concerning emphysema she was also cautious. In addition, Morgan discussed to some extent the possibility of an increased exposure due to smoking. This question is dealt with in detail in section 3.2 of our report. Finally, Morgan meant that her findings, for cancer at least, may have been coincidental rather than etiologic, but she had the opinion that additional studies are clearly needed.

There seem to have been no studies made concerning any possible association between cadmium exposure and cancer of the gastrointestinal tract. The incidence of stomach cancer in Japan is extremely high, however. According to the data on cancer incidence in five continents (Doll, Muir and Waterhouse, 1970), the age standardized incidence rates (5 year groups in the age range from 35 to 64 years old standardized against a world standard population) for males in two prefectures in Japan are 156 and 164, respectively, per 100,000. These are by far the highest incidence rates found in all of the countries studied. Next in order comes Cape Prov, South Africa (Colored population), with an incidence rate of 102 per 100,000. Other countries have a much lower incidence rate of stomach cancer, as a rule between 20 and 40 per 100,000. Available data from the contintental U.S.A. show values between 11 and 33, while the Japanese and Hawaiian populations of Hawaii have incidence rates of 62 and 80, respectively. The incidence rate in Sweden is 28 per 100,000. The incidence rate for women is generally lower, but in Japan the rate remains high (80 per 100,000 as compared to a usual 20 per 100,000 in other countries).

The high incidence of stomach cancer in Japan, of course, is no proof whatsoever that cadmium has some causal connection with stomach cancer. The obvious exposure to cadmium via food in Japan (8.4.1.12 and 8.4.2.1.2) should, however, motivate further studies.

7.2 GENETIC EFFECTS

Little information is available concerning possible genetic effects of cadmium and cadmium compounds. Preliminary genetic experiments with $CdCl_2$ on Drosophila melanogaster were performed by Ramel and K. Friberg (personal communication). Larvae were treated with 62 mg/l substrate, which was the maximum dose in toxicity test giving a delay of larval development without causing an excessive lethality. As an indication of chromosome breakage, the frequency of sex chromosome loss was used. One experiment was also performed on the combined effect of $CdCl_2$ and 3000 r X-irradiation on sex-linked recessive lethals. The treatment with cadmium compound was given as mentioned above. The results of these two experiments (table 7:2 and 7:3) do not indicate any significant effect of $CdCl_2$ on chromosome breakage, induction of recessive lethals or on chromosome repair mechanism. It must be stressed, however, that the material is small and further investigations are needed.

7.3 CONCLUSIONS

The studies on animals show without doubt that cadmium and cadmium compounds can give rise to malignant tumors in rats. The carcinogenic evidence of cadmium in human beings is by no means conclusive as yet but fully motivates further and intensified studies in groups exposed industrially as well as through food and ambient air. Very few genetic studies have been performed. In one study on Drosophila, no significant genetic effects could be seen. In view of other known effects of cadmium and its accumulation in the human body, there is a great need for further studies.

Table 7:1 CONCENTRATIONS OF CADMIUM IN LIVER AND KIDNEYS (µg/g ash) IN PATIENTS (average age: 60) DYING FROM CANCER OF THE LUNG AND OTHER FORMS OF CANCER AND IN CONTROLS (from Morgan, 1970).

	Number examined	Liver		Kidneys	
		Mean	S.D.	Mean	S.D.
Cancer of the lung	55	254	133	3513	1587
Other forms of cancer	50	179	140	2937	2065
Controls	47	182	99	2406	1299

Table 7:2 SEX CHROMOSOME LOSS (XO-males) AFTER LARVAL TREATMENT WITH 62 mg $CdCl_2$ / 1 IN THE SUBSTRATE (Ramel and K. Friberg, unpublished data).

	$CdCl_2$		Control	
Egg laying period in days after treatment	Total number counted	Per cent sex chromosome loss (XO-males)	Total number counted	Per cent sex chromosome loss (XO-males)
0 - 2	1,708	0.5	2,573	0.3
2 - 4	3,858	0.4	5,007	0.1
4 - 6	4,833	0.1	5,609	0.3
6 - 8	4,331	0.2	5,365	0.3
8 - 10	3,913	0.3	4,423	0.2
10 - 12	4,717	0.4	5,166	0.3
0 - 12	23,360	0.3	28,143	0.2

Table 7:3 THE EFFECT OF $CdCl_2$ (larval treatment with 62 mg $CdCl_2$ / 1 in the substrate) ON RECESSIVE SEX-LINKED LETHALS IN MULLER-5 TEST AFTER 3000 r X-RAYS TO MALES. (Ramel and K. Friberg, unpublished data).

	$CdCl_2$		Control	
Egg laying period in days after treatment	Number of X-Chromosomes tested	Per cent recessive lethals	Number of X-Chromosomes tested	Per cent recessive lethals
0 - 2	235	10.6	149	11.3
2 - 4	445	7.7	190	5.8
4 - 6	80	17.5	98	6.1
6 - 8	285	4.2	305	3.6
0 - 8	1,045	8.1	742	6.1

CHAPTER 8

THE ITAI-ITAI DISEASE

8.1 INTRODUCTION

In 1946, Doctor Hagino, a general practitioner returning from the war, re-opened a private clinic, in operation in Fuchi-machi, Toyama Prefecture, since his grandfather's time. Dr. Hagino was visited by patients with a painful disease, which he called the "Itai-itai byo", (meaning ouch-ouch disease). The disease had occurred endemically in the area for several years and is probably identical with a "rheumatic disease" described by Nagasawa et al., 1947, among inhabitants of Miya-gawa-mura in the Toyama Prefecture. It was noted that the disease had a relationship with the water of the Jintsu River and that a certain Kamioka mine upstream often caused damage to crops. Drs. Hagino, Kobayashi and Yoshioka, examining river water, rice and fish, could demonstrate high concentrations of certain heavy metals, particularly cadmium. The location of the endemic area is seen in figure 8:1.

Hagino and Kono reported about the Itai-itai disease at the 17th meeting of Nihon-Rinsho-Geka-Ikai (The Japanese Society of Clinican Surgeons) in 1955, making the first official use of the name (Kato and Kono, 1968). The same year, Hagino et al. reported on the disease at the 9th Hokuriku Medical Congress (Hagino, 1969a). In 1961, Hagino and Yoshioka reported that heavy metals, especially cadmium, would play an important part as etiological factors of the disease (Kato and Kono, 1968). Epidemiological and clinical studies were started on a larger scale in the 1960's by groups supported by the Japanese government. The Japanese Ministry of Health and Welfare in 1968 declared, "The Itai-itai disease is caused by chronic cadmium poisoning, on condition of the existence of such inducing factors as pregnancy, lactation, unbalanced internal secretion, aging, deficiency of calcium, etc."

8.2 CLINICAL FEATURES

8.2.1 Symptoms and signs

The clinical course of the disease has been described by Takase, et al., 1967 (summarized in English by Tsuchiya, 1969), Hagino, 1968a and b, 1969a, Ishizaki, 1969b, Murata et al., 1969, 1970, and Tsuchiya, 1969. The greatest number of the patients have been treated by Hagino and/or Murata. Figure 8:18 shows a patient with advanced skeletal deformities. Figure 8:19 shows multiple pseudofractures on X-ray of the ribs in one patient, (Murata personal communication).

From Murata et al., 1970, the clinical manifestations can be summarized as follows. Most of the patients are postmenopausal women with several deliveries (average: 6). The most characteristic features of the disease are lumbar pains and leg myalgia. Pressure on bones, especially the femurs, backbone and ribs produces further pain. Another characteristic of the disease is a waddling gait caused by bone deformation. Such conditions continue several years until one day the patient experiences a mild trauma and finds herself unable to walk. She is then confined to bed and the clinical conditions progress rapidly. Not only the bones of the extremities but also the ribs and other bones are susceptible to multiple fractures after very slight trauma such as coughing. Skeletal deformation takes place, with a marked decrease in body height.

8.2.2 Laboratory examinations

8.2.2.1 Blood findings

Blood examination has shown hypochromic anemia in most patients. Serum-Fe levels have been low in many. The erythrocyte sedimentation rate has been elevated in some. Almost no deviation from the normal has been observed in serum protein and albumin/globulin ratios. The levels of calcium and inorganic phosphorus in serum are often low, while the alkaline phosphatase level is high. Data from studies by Murata et al., 1970 are shown in figure 8:2.

8.2.2.2 Urinary findings and renal function tests

Proteinuria has always been found. In most cases, glucosuria has also been present. While urinary calcium levels have been normal, urinary phosphate has been reduced. The urinary amino acid levels have been above normal (Takase et al., 1967, Takeuchi et al., 1968, Ishizaki, 1969b, Murata et al., 1969 and Tsuchiya, 1969).

Quantitative determinations have shown an increase in cadmium concentration and a decrease in zinc concentration in blood and urine, in comparison with control subjects (see, for example, Murata et al., 1970 and figure 8:11 from Ishizaki, 1969b).

In Itai-itai disease, proteinuria, glucosuria and amino-aciduria are considered signs of renal dysfunction. On separation by paper electrophoresis, a typical tubular protein pattern occurs in cases of Itai-itai disease and also in the preceding stages (proteinuria without bone changes), as shown recently (Piscator and Tsuchiya, unpublished data). They examined 10 female patients with Itai-itai disease and 12 persons (10 women and 2 men) from the endemic area with only proteinuria and glucosuria. The pattern found was similar to that observed in chronic occupational cadmium pcisoning. In figure 8:3 some of these patterns are shown (compare with figure 6:2).

Further evidence that the proteinuria observed in women in the endemic district is similar to the one seen in workers exposed to cadmium and distinctly different from the one seen in glomerular disease is shown in figure 8:4 (Piscator and Tsuchiya, unpublished data). The figure shows patterns of urinary proteins separated by electrophoresis in polyacrylamide gel (disc-electrophoresis).

Still further evidence that the proteinuria is of a tubular type has been obtained by using gel filtration on Sephadex G-100, (Piscator and Tsuchiya, unpublished data). The main part of the urine proteins from cases and suspected cases of Itai-itai had molecular weights less than that of albumin. Among these low molecular weight proteins, immune globulin chains and β2-microglobulin were found, as has earlier been demonstrated in cadmium workers by Piscator, 1966.

Electrophoretic examinations of urine proteins have also been performed by Fukushima and Sugita, 1970. In 8 patients, they found a relatively small percentage of albumin and a dominance of α2- β- and γ-proteins, also indicating a tubular type of proteinuria.

Takeuchi et al., 1968, and Murata et al., 1970 investigated 4 and 3 patients,respectively, with Itai-itai disease especially concerning renal function. They stated that tubular function defects were found, whereas glomerular involvement was not detected.

8.2.3 Histo-pathological changes

The following, though very incomplete, are the only data on histological changes available to us (for cadmium concentrations in organs, see section 8.4.1.11).

8.2.3.1 Kidneys

Kajikawa et al., 1957, found in two resections senile arteriosclerotic contracted kidneys and nephropyelitis. Takeuchi et al., 1968, found in biopsy specimens from three patients no marked changes in the glomerules. In the tubules, atrophic changes, with flattening of the epithelium, were seen.

8.2.3.2 Bone

Ishizaki, 1969b, citing Kajikawa et al., 1957, and his own material, has described histological findings in bone from autopsies. The changes have been consistent with those found in osteomalacia. X-ray findings were also characteristic of osteomalacia. On the basis of two resected cases and biopsy of seven cases, Ishizaki and Fukushima, 1968, (quoting findings by Kajikawa et al., 1957) concluded that the main pathological and histological findings were characteristic of osteoid formation and osteoporosis. Kono et al., 1961, found the Itai-itai disease very similar to common forms of osteomalacia. However, they found fewer osteoblasts in Itai-itai disease biopses than usually found in osteomalacia.

8.3 DIAGNOSIS

Ishizaki and Fukushima, 1968, discussed the clinical diagnosis of Itai-itai disease. They pointed out that the first and second stages could reasonably be considered to be renal dysfunction and bone changes, respectively. However, even if a specific diagnosis of renal impairment were possible, patients so diagnosed who can carry out their daily lives unhampered until bone symptoms develop cannot from a practical standpoint be included in the Itai-itai group. Because the subjective symptoms and the bone signs clinically observable through X-rays are very unspecific in the early stages, the diagnosis at that time could reasonably be based on blood signs of osteomalacia, including increased alkaline phosphatase and decreased serum inorganic phosphate. The authors pointed out that a roentgenological diagnosis would not be helpful in the early stages because detectable X-ray changes would not be evident until the disease has developed to some extent. Moreover, as the disease is frequent in menopause and in old age, menopausal or senile osteoporosis could be mixed with the Itai-itai disease. To avoid such mistakes, it should be necessary to require specific signs of osteomalacia (Milkman's pseudofracture) for the roentgenological diagnosis of Itai-itai disease.

Based on elaborate discussions, the Itai-itai disease research group of 1962-1965 has worked out a standard for the diagnosis of Itai-itai disease, to be used in the epidemiological research (Kato and Kono, 1968). The following observations should be noted:

A. Subjective symptoms
   1. Pain (lumbago, back pain, joint pain)
   2. Disturbance of gait (duck gait)

B. Physical examination
   1. Pain by pressure
   2. "Dwarfism"
   3. Kyphosis
   4. Restriction of spinal movement

C. X-ray
   1. Milkman's pseudofractures
   2. Fractures (including callus formation)
   3. Thinned bone cortex
   4. Decalcification
   5. Deformation
   6. Fish-bone vertebrae
   7. Coxa vara

D. Urine analysis
   1. Coinciding positive tests for protein and glucose
   2. Protein (+)
   3. Glucose (+)
   4. Decreased phosphorus /calcium ratio

E. Serum analysis
   1. Increased alkaline phosphatase
   2. Decreased serum inorganic phosphate

The subjects are classified into the following five groups:

I: Surely Itai-itai patients
i: People deeply suspected for Itai-itai disease
(i): People suspected for Itai-itai disease
(O): People needing follow-up
O: People with no suspicion of Itai-itai disease

The methods for diagnosis differed a little with each year, as stated in Kato and Kono, 1968, and a sixth group (I) is sometimes named. In some reports the groups are defined as follows (Ishizaki and Fukushima, 1968, and Fukushima, personal communication):

I: Patient (typical bone manifestations on X-ray)
(I): Person cured of Itai-itai disease
i: Person deeply suspected (bone signs but not typical + glucosuria + proteinuria + increased alkaline phosphatase)
(i): Person suspected (slight bone signs on X-ray + proteinuria + glucosuria + increased alkaline phosphatase)
O_{ob}: Person with need for continuous observation (urinary and/or blood signs)
O: Person with no suspicion

Sometimes only the I-type of patients is meant when the "number of patients" is discussed, but in other circumstances, other groups are also included in the "patients".

The question of the differential diagnosis of Itai-itai disease has later been taken up in more detail by a study group organized by the Japanese Association of Public Health in connection with an evaluation of some suspected cases of Itai-itai disease. As the criteria applied have no direct bearing upon the material referred to in the present report, they are not commented upon. For further information, reference is made to a publication by the Japanese Association of Public Health, 1970a.

8.4 EPIDEMIOLOGY

Since the Itai-itai disease was first discovered in the Toyama Prefecture, the most detailed epidemiological studies have been performed in this area. However, the Japanese Ministry of Health has recently promoted studies in other areas where exposure to cadmium occurs. The studies in the Toyama area and thereafter in other areas will be described.

8.4.1 Epidemiological studies in Toyama Prefecture

8.4.1.1 1962-1965 Epidemiological research

The limited research on the epidemiology of the disease prior to 1963 must be classified as preliminary or pilot studies. Since no diagnostic standard had been agreed upon, the different studies defined the disease differently. An epidemiological survey made between 1962 and 1965 in Fuchu-machi, Toyama City, Osawano-cho, Yatsu, Nyuzen-cho, and Tonami City was evaluated according to the 1963 diagnostic standard (Kato and Kono, 1968). All of these places are in the Toyama Prefecture. All females over 40 years of age were selected, except in Tonami City, where males over 40 years of age were also included in the 1,100 subjects examined. Under examination of a total of 3,645 subjects, 28 patients, 14 deeply suspected and 19 suspected subjects had been found by 1965 in the endemic districts located along the Jintsu River. (see table 8:1). On the other hand, in Ota (Toyama City), located along another river in the endemic district, neither patients nor suspected patients were found among the 508 females over 40 years of age, 334 of whom were examined in 1964 in the same way as in the endemic districts. Also in Tonami City and Nyuzen-cho, located along other rivers in Toyama Prefecture, neither patients nor suspected patients were observed. These studies made clear that the Itai-itai disease was found only in specific districts in the Jintsu River basin. Further epidemiological research therefore was concentrated along this river.

8.4.1.2 1967 Epidemiological research

In 1967, a larger, better structured epidemiological study was performed by the Toyama Prefecture Health Authorities in co-operation with Kanazawa University in an attempt to find and to treat all Itai-itai patients (the data under this section are from Kato and Kono, 1968, and Ishizaki, personal communication, unless otherwise stated).

8.4.1.2.1 Groups studied and selection of subjects for final diagnostic procedure

A total of 6,717 subjects, all inhabitants over 30 years of age and of both sexes of Fuchu-machi, certain parts of Toyama City, Osawa-cho and Yatsuo-cho, were included in the first screening made by a questionnaire, seen in table 8:2, and by semi-quantitative determination of protein and glucose in urine. This screening was performed on 6,114 persons, 91 percent of the 6,717 subjects originally selected for the study,

Based on the results of the first screening, 1,911 persons were selected for the second examination according to the procedure referred to in figure 8:5. Out of the 1,911 people selected for the second examination, 1,400 underwent the examination, which included a medical interview, general clinical examination, and X-ray of the right upper arm and shoulder. As a result of the second examination, 451 persons were selected for a final examination. The exact basis for this selection has not been possible to elucidate, but among important criteria were bone changes.

8.4.1.2.2 Final diagnostic examination (Third examination)

Out of the 451 persons selected for a final examination, 419 were examined. The examination included a medical interview, X-ray of the pubic region, orthopedic examination, urine analysis for glucose, protein, calcium, phosphorus, creatinine, cadmium, lead, and zinc, as well as serum analysis of alkaline phosphatase and inorganic phosphorus. All of these analyses were not performed on all persons.

8.4.1.3 Total number of cases of Itai-itai disease

It is not possible to precise a figure on the incidence of Itai-itai disease over the years. The 1967 epidemiological survey is cross-sectional, giving only prevalence data at the time of the study. It is estimated that nearly 100 deaths due to the Itai-itai disease have occurred up until the end of 1965 (Yamagata and Shigematsu, 1970). The following numbers of persons with Itai-itai disease were found: I:50, i:17, (i): 31 and O_{ob}:136. See table 8:3 (from Ishizaki and Fukushima, 1968) for the distribution of examined persons according to place of residence, sex and age. The abbreviations for groups as used in this particular report are explained in table 8:1. The Toyama Prefectural Health Authorities now continuously register all living patients. Several new cases have been diagnosed since the 1967 study. Figures from September, 1968, are given in table 8:4.

The latest available figures on the total number of cases are stated by Ishizaki, 1969c, as, until the end of 1968, 57 patients, 56 suspected, and 200 requiring observation. However, these figures are not directly comparable to those in tables 8:3 and 8:4 because Ishizaki defined the groups somewhat differently than earlier. The "observation group" included subjects who had recovered.

8.4.1.4 Age and sex

According to table 8:4 from September, 1968, only one male was placed in the group of patients. However, according to the 1967 epidemiological research, 5 male patients or suspected patients were found, as seen in table 8:3. The reason for the registration of only one male patient in the table from September, 1968, is not clear. Among the observation subjects there were an appreciable number of men.

Noting the age distribution in table 8:3 from the 1967 report, one can conclude that the osteomalacia has been found only in women of 45 years of age or older. No patient was found in the age group below 44 years, but two observation cases were registered.

8.4.1.5 Frequency of new cases of Itai-itai disease

Hagino (personal communication) had the impression that the frequency of disease onsets was higher in the 1950-1960 period than in the 1960-1970 period. At the same time, he pointed out that a number of cases not known before are still diagnosed yearly.

By means of the 1967 epidemiological research and the subsequent registration of all patients by the Toyama Prefectural Health Authorities, a year of onset was estimated for each patient, as seen in table 8:5. From this data, it is evident that a majority of the presently registered patients first complained of symptoms in the period between 1945-1964 but 10-15 percent did not complain of symptoms until 1965 or later. As many Itai-itai patients who contracted the disease several years ago must have died by 1968 (see 8.4.1.3), great caution must be exercised in interpreting the data.

8.4.1.6 Geographical distribution of Itai-itai patients

The locations of the different population centers within the Toyama Prefecture are seen on the maps in figures 8:1 and 8:6.

It has become evident from the research that the disease has only been found in a limited area around the parts of the Jintsu River near Toyama City, where its water is used for irrigation of rice fields. The prevalence of the Itai-itai disease in different parts of the endemic area has been best illustrated by the detailed survey of 1967, the results of which can be seen in figure 8:6, from Ishizaki and Fukushima, 1968. The frequency of the disease is there illustrated by the percentage of women over 50 years of age having or suspected of having the Itai-itai disease. The 1967 research group also analyzed the cadmium concentration in the upper stratum of the soil in the paddy fields (see 8.4.1.12) and found a striking correlation with the prevalence of the Itai-itai disease, even within the endemic area (see figures 8:6)and 8:7).

8.4.1.7 Prevalence of proteinuria and glucosuria

In addition to sure or suspected cases of Itai-itai disease, a great number of persons with proteinuria and/or glucosuria have been found in connection with the 1967 epidemiological studies. The total prevalence of proteinuria (sulfosalicylic acid, trichloracetic acid or testtape) and glucosuria (Benedict's reaction) in males and females and in different age groups is shown in figure 8:8 from Ishizaki, 1969b. The number of persons examined is given in table 8:6 (Ishizaki, personal communication).

As can be seen, about 50 percent or more of inhabitants older than 60 in the endemic area had proteinuria. Among those over 70, 70-80 percent had proteinuria. The prevalence was somewhat higher among females. The prevalence for both sexes was considerably higher than in a non-endemic area of the Toyama Prefecture. However, even in such a non-endemic district, the prevalence was high, especially in women. Thus, about 20 percent or more of women older than 60 and 30-40 percent older than 70 in non-endemic districts had proteinuria. From the methodological point of view, exactly comparable figures from other parts of Japan are not available. In a study of the epidemiology of proteinuria on about 5,000 persons from Hiroshima and Nagasaki (comprising a portion of the clinical sample under study at the Atomic Bomb Casualty Commission), however, considerably lower prevalence data were found. The methods used were sulfosalicylic acid or testtape and positive reactions were confirmed with nitric acid. Results of the study are seen in table 8:7. The results of the study of people living on Tsushima Island (section 8.4.2.1) also showed considerably lower prevalence of proteinuria in the non-contaminated areas.

Since either proteinuria or glucosuria can indicate a renal tubular impairment, the occurrence of both in a person is a stronger indication of such a renal defect. The concurrent appearance of these two conditions in different age groups in different areas of the Toyama Prefecture is shown in figure 8:9. Whereas the frequency in age groups up to 45 years has not been different from that found in a non-endemic area, a very clear difference can be seen in age groups of 55 years and older, in both women and men. No information on the number of persons examined is available. Concurrent glucosuria and proteinuria in women of the endemic area can also be seen in figure 8:10. The women born and spending their lives in the endemic area have had a higher prevalence of proteinuria and glucosuria than women born elsewhere but living in the endemic area at least 20 years. It is not known whether or not the differences are statistically significant.

8.4.1.8 Hereditary and dietary factors

8.4.1.8.1 Hereditary factors

Dent, 1956, has described a number of renal tubular reabsorption defects based on heredity which have given rise to osteomalacia. Therefore it is of interest to seek evidence of similar hereditary factors in the Itai-itai disease. Ishizaki, 1969b, reported that in many families in the endemic district, both the farmer's mother and wife had contracted the disease. No cases had occurred in women from the endemic district who had married and moved to a family in the non-endemic district. These facts indicate that the etiology rests on environmental rather than hereditary factors.

8.4.1.8.2 Dietary factors

The classical form of osteomalacia is based on a deficiency of Vitamin D. In the beginning of the research on the Itai-itai disease, dietary and climatological factors were assumed to play an important role in its etiology.

The Toyama Prefectural Health Authorities performed a survey on the dietary conditions in 200 households in the endemic area during 1955-1956. The results are given in table 8:8. For comparison, averages for Sweden in 1960 are also given. It is evident that the dietary standard in the Itai-itai patients' homes and in the endemic area as a whole is not much different from the mean in the Toyama Prefecture or from the Japanese average. It is not known to what extent the figures for the different areas in Japan are comparable to the figures for Sweden, but for certain dietary components, the large differences noted are not likely to disappear, even if the figures are corrected for the different methods of calculation. As Vitamin D is a known essential dietary factor when discussing osteomalacia, it is unfortunate that no Japanese figures for this vitamin are available. The Vitamin A and fat intakes in the Itai-itai patients are lower than the Japanese average and considerably lower than the Swedish average. It is therefore probable that the Vitamin D intake is also lower. If such is the case, a great exposure to sunlight could compensate for the low intake of Vitamin D. However, since the endemic area has a rainy climate, and since the women dress in such a way that they screen off a great part of the sunshine, this compensation is not likely. A higher calcium intake could also partly compensate for a low level of Vitamin D, but the calcium intake in Japan is very low. The figures from the investigation of 1955-1956 in the homes of the Itai-itai patients represented a mean intake for all family members. Several investigations in various countries have shown that the calcium intake is usually much lower in women and therefore it is likely that the women in the endemic area consume significantly less calcium than indicated by the figures.

It must also be remembered that the nutritional situation in Japan during and immediately after the Second World War was poor. Insull, Oiso and Tsuchiya, 1968, documented acute generalized malnutrition problems arising in 1936 and 1945. They cited evidence showing that the heights of children during and directly after the war were significantly retarded.

8.4.1.9 Profession and other factors

In connection with the 1967 epidemiological study, information on certain socio-economic factors about Itai-itai patients and "controls" was obtained (Ishizaki, personal communication). For each Itai-itai patient, a "control", matched for age and sex and living in the endemic area very close to the patient, was chosen. The results are given in table 8:9. There are certain differences between the groups. The patients had lived longer in the same area, had had more pregnancies, had drunk water from the Jintsu River to a greater extent, and had lower incomes. No information was given on, for example, the occurrence of proteinuria and/or glucosuria in controls.

8.4.1.10 Concentrations of heavy metals in urine

The 1962-1965 research group analysed urine from inhabitants of different parts of the Toyama Prefecture. The method of sampling in the various patient categories can not be known through literature available to us. Values reported, however, showed that cadmium concentrations in urine from persons in the endemic area were higher than from persons in other parts of the Toyama Prefecture, (Ishizaki et al., 1965, Tsuchiya, 1969, and Ishizaki, 1969a). Lead and zinc values, on the other hand, showed no geographical differences (Ishizaki et al., 1965, and Tsuchiya, 1969). The 1967 research group, as referred to in Ishizaki's report, 1969b, also analyzed urine concentrations of cadmium (probably by atomic absorption after extraction). Increased concentrations were found in persons coming originally from the endemic area (see figure 8:11).

8.4.1.11 Concentrations of cadmium in organs

Few values of cadmium in organs from Itai-itai patients have been reported. Some early data from one patient described concentrations in bones. However, in this case, the different organs had been stored together in formaldehyde for several years, (Kobayashi, personal communication), so that the values must be considered unreliable.

Ishizaki, Fukushima and Sakamoto, 1970b, reported organ values (atomic absorption) from autopsies on four Itai-itai patients. The results are given in table 8:10. Formaldehyde preservations were not used. At the same time, cadmium analyses were performed on organs from 38 controls who died in hospitals in Kanazawa. All of them had been living in non-endemic areas in or near Kanazawa. Results are shown in figure 8:12. As can be seen by comparing table 8:10 with figure 8:12, the cadmium content of the liver was 5-10 times higher in Itai-itai patients than in the controls in the same age group. The patients' kidney values, however, were lower than those of the controls. The authors stated that the low kidney values in the Itai-itai patients could be explained by the advanced kidney damage. The values given should also be compared with "normal values" from Japan and other countries and with data from workers industrially exposed, with signs of cadmium poisoning, (see 4.3.2.1 and 4.3.2.2). Such a comparison stresses the accumulation of cadmium in liver and pancreas of the Itai-itai patients.

8.4.1.12 Concentrations of heavy metals in the environment

As has been discussed, most of the Itai-itai patients displayed their symptoms many years ago. If heavy metals caused the disease, even exposure several decades earlier must have been of importance. However, no quantitative information on such exposure is available.

After the theory about cadmium as a cause of the Itai-itai disease was advanced, the Jintsu River became suspected as the carrier of the cadmium from the Kamioka mine to the endemic area. Kobayashi, 1970, stated that the increased production at the mine together with faulty treatment of waste water polluted the Jintsu River heavily during the Second World War. He explained that particles carried by the river became deposited in the rice fields. Damage to the rice crop prompted a severe dispute between the farmers and the owners of the mine. Ishizaki's studies (personal communication) on cadmium content in year rings from cedar trees may also speak in favor of a higher concentration of cadmium in the Jintsu River several years ago.

In 1959 Kobayashi and Yoshioka, as cited in a report by Yamagata and Shigematsu, 1970, analyzed samples of rice from the endemic area. Values (ppm in ash) in polished rice were given as 120-350 ppm in exposed areas, compared with 21 ppm in a control area. In the root of rice plants, corresponding figures were 690-1300 and 35 ppm, respectively. No information about the representativeness of the samples was reported.

In 1967, a study headed by Shigematsu on the distribution of cadmium in the endemic area was made under a grant from the Ministry of Health and Welfare. This study is included in the above mentioned report by Yamagata and Shigematsu, 1970. In water upstream from the Kamioka mine and tributaries of the Jintsu River, cadmium was detected in trace amounts or not at all in the samples taken. In water downstream from the mine, a maximum value of 0.009 ppm was found. Out of four samples from the drainage from the mine, three contained 0.005-0.06 ppm (pH about 7-8) and one contained 4 ppm (pH 2.8) of cadmium. Near the drainage area of the mine, cadmium concentrations of 363 and 382 ppm were found in suspended materials.

Samples of paddy soils irrigated with water from the Jintsu River and from its tributaries, respectively, were analyzed. The comparison of concentrations of cadmium found is shown in figure 8:7. The river-irrigated soil showed a much higher concentration. In figure 8:6, the prevalence of sure or suspected cases of Itai-itai disease in different areas around the Jintsu River and tributaries is shown. When figures 8:7 and 8:6 are considered together, the association between high concentrations of cadmium in the paddy soils and the Itai-itai disease is obvious.

Yamagata and Shigematsu also reported cadmium concentrations in unpolished rice. Samples from paddy fields irrigated with water from the Jintsu River contained 0.35-3.36 ppm (average: 1.0, wet weight), while samples from paddy fields irrigated with water from the tributaries showed much lower values, with a maximum concentration of 0.11 ppm. The normal concentration of cadmium in polished rice from all areas in Japan has shown an average value of 0.07 ppm. Ishizaki, Fukushima and Sakamoto, 1970a, reported cadmium content in 340 samples of foodstuffs on the market in Japan as a whole. The reported cadmium levels in grain and vegetables were not higher than those in the United States and in Germany. Organs of sea mollusca and crustacea contained high levels of cadmium. Very high values were observed in livers of some sea mollusca, for example, 10-110 ppm (wet weight) in some cuttlefish and 92-420 ppm in Babylonia Japonica, a roll shell. These findings are in agreement with the known accumulation of several elements, including cadmium, by mollusks (see e.g., Pringle et al., 1968).

Based on the National Nutrition Survey of 1966 and on available data on cadmium content in food, a representative value for the daily intake of cadmium in a Japanese diet has been estimated as 60 µg by Yamagata and Shigematsu, 1970. A breakdown of the 60 µg indicated that 23 µg of cadmium should come from an intake of 335 g of polished rice with a concentration of 0.07 ppm. The daily intake of cadmium in the endemic area was calculated as 600 µg by assuming an average cadmium concentration in rice of 1 ppm and a concentration in other foodstuffs produced and consumed locally about 10 times the value for Japan as a whole.

8.4.2 Other areas in Japan under survey for Itai-itai disease

The occurrence of the Itai-itai disease along the Jintsu River with cadmium as a suspected cause has stimulated a search for signs of cadmium intoxication in other areas contaminated with cadmium. Figure 8:13 shows the distribution of mines dealing with sulphide ores of copper, lead and zinc as well as smelting works. The figure also shows four areas, apart from the Jintsu River basin, selected for more detailed study. In a statement of March 27, 1969, the Ministry of Health and Welfare defined these as the coastal areas of the Namari River and the Nihazama River in Miyagi Prefecture, the Usui River and the Yanase River in Gumma Prefecture, and the Sasu River and the Shiine River on Tsushima Island of Nagasaki Prefecture. On May 28, 1969, the coastal area of the Okudake River of Ooita Prefecture was also included. A considerable amount of information from Tsushima Island has been made available to us.

8.4.2.1 Sasu and Shiine basins, Tsushima Island, Nagasaki Prefecture

8.4.2.1.1 Medical examinations

Preliminary medical studies were carried out in 1965. The results pointed out that Kashine, downstream from a mine in the River Sasu basin, was a most suspect area. New studies were performed in 1968, and on a more comprehensive basis, in 1969. The results of the last mentioned study are available in a report by the Department of Health, Nagasaki Prefecture, March, 1970.[x/] The medical examinations were carried out by the staff of the Section of Health, Izuhara. Urine analyses were made at the Laboratory of Hygienic Chemistry, Faculty of Pharmaceutical Sciences, Nagasaki University.

The area under investigation consists of a control area: the village Are in the basin of the Are River and of an observation area: villages in the basins of the rivers Sasu and Shiine; Hikage-Kamiyama (including Ohita, Kyozuka, Jifu, Himi and Wakata), Shimobaru (including Tokoya and Nagon), Komoda (including Komoda-hama), Shiine (including Shiine-hama) and

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[x/] The report was translated into English through the curtesy of Professor Eigo Takabatake, Faculty of Pharmaceutical Sciences, Nagasaki University.

Kashine (including Uragochi). This area can be seen in figure 8:14.

In the area under observation, 653 people over 40 years of age had been living for at least 5 years. The corresponding number for the control area was 176. Out of a total of 829 subjects, 541 were medically examined. The number of subjects and the absolute and relative number examined in different areas divided into men and women and into different age groups are given in table 8:11. As can be seen, the relative number examined differed considerably among the different areas. This variation is not so marked for women but for men it is noteworthy that only 20 percent of those living in the control area, Are, participated. It was not stated in the report whether or not the examined and the non-examined persons differed from each other in any way.

The investigation included an interview, urinary protein (testtape) and glucose (testtape) determinations, X-ray examination of chest, and analyses of urinary content of cadmium. The protein and glucose examinations were performed on 522 subjects. The results are given in table 8:12. There is a considerably higher prevalence of both proteinuria and glucosuria in the Kashine, Shiine area than in the other areas.

In the report, prevalence of proteinuria in different age groups is given for the areas grouped as follows: Kashine and Shiine, Shimobaru and Komoda, Hikage-Kamiyama and Are. The results can be seen in figures 8:15 and 8:16. It is not possible from the report to know the exact number in the various age groups. If the fact that protein examinations were carried out on only 522 of the 541 subjects examined is not considered, the age distribution will be as shown in table 8:13.

No cases of Itai-itai disease with bone changes were diagnosed. It is not clear how many persons were examined with regard to chest X-ray and cadmium analyses. Concerning possible exposure to cadmium, note in figure 8:14 that Hikage and Kamiyama are upstream from the mines.

Figures 8:15 and 8:16 undoubtedly show a considerable difference between the Kashine-Shiine areas and the other areas. The difference increases with age and time of residence in the area. The increased prevalence of proteinuria is found in both men and women. One must stress, however, that the number of examined subjects in some groups was extremely small, which invalidates any precise interpretation of the data. Furthermore, the percentage of residents participating in the examination differed from area to area. As has been mentioned above, only 20 percent of the men in Are were examined. The bias of differences in the participation in the different areas can not be evaluated in detail. We see no reason, however, that the differences found in prevalence of proteinuria and glucosuria was due to any substantial degree to differences in participation in the examinations.

From the report it is possible to separate farmers from other occupational groups. The numbers are too small to divide into age groups, but the total prevalence of proteinuria and glucosuria in farmers is presented in table 8:14. The high prevalence of proteinuria and glucosuria among both sexes in the Kashine-Shiine areas is again apparent.

Urinary cadmium analyses (atomic absorption after extraction) were carried out on 45 of the persons who had had positive results for protein and/or glucose. Results of these examinations are shown in figure 8:17. As can be seen, the cadmium levels are high, particularly in the Kashine area.

From the group of men and women in Kashine with positive test results for protein and/or glucose in urine but without hypertension, nine were selected for more detailed examination. The results were discussed within the group dealing with the differential diagnosis of Itai-itai disease (Japanese Association of Public Health, 1970a).

Three women, aged 47-67 years, agreed to hospitalization. Detailed examinations were carried out, including tests of renal and hepatic function, determination of electrolytes in serum and urine, determination of cadmium in urine, electrophoretic separations of serum and urine proteins, urine cultures, pyelography, renograms and renal biopsy.

In one woman (47 years of age) with a daily excretion of 780 mg protein, the electrophoretic pattern of the urinary proteins was typical for a tubular proteinuria. She excreted more than 30 μg of cadmium per day. Urine culture was negative. Histological examination of renal tissue obtained by biopsy showed slight changes mainly in the proximal tubules. There were no marked changes in the interstitial tissue. Creatinine clearance was normal, whereas the PSP-test showed tubular impairment. The study team concluded that this was a case of pelvic nephritis. It is of course difficult to make a detailed evaluation on the basis only of the information in the publication. It seems, however, that this patient showed many findings typical for chronic cadmium poisoning.

The other two patients are more difficult to evaluate, but they had a decreased PSP-excretion, which would indicate tubular impairment. In one patient (67 years of age), the electrophoretic pattern of the urinary proteins was of a mixed glomerular-tubular type. Urinary protein excretion was 900 mg/day. Histological examination of renal tissue showed no marked changes in the glomeruli but showed slight changes in the tubules. This patient was judged by the study team to be suffering from senile nephrosclerosis, but also in this case we would not exclude cadmium as the cause of the tubular impairment. The third patient (55 years of age) was diagnosed as having pelvic nephritis. The electrophoretic pattern was of a more glomerular type and bacteria were found in the urine.

8.4.2.1.2 Cadmium exposure

Data concerning the concentration of cadmium in foodstuffs have been obtained partly from personal communications with representatives for the Department of Health, Nagasaki Prefecture and partly from a published report (Japanese Association of Public Health, 1970b), giving results from a cooperative study on uptake and accumulation of cadmium in areas under observation. In the cooperative study, headed by I. Shigematsu, the measured values from the various prefectural institutes were cross-checked and considered to agree fairly well, so that it was considered possible to refer to the figures without correction.

The data from the Tsushima Island covered 23 samples of self-stored rice and 19 samples of self-produced bean paste from 22 families in the contaminated areas and 9 families in the control area. The average concentration of cadmium in rice (ppm, dry weight) in the contaminated areas taken as a whole was 0.37 ppm (range: 0.03-1.02). In the control area, Are, the average content was 0.08 ppm (range: 0.02-0.15). The content of cadmium in rice as well as in bean paste for the different areas under observation and for the control area, Are, is seen in table 8:15. For other foodstuffs, the different areas can not be compared in a similar way, but the control area can be compared with all other areas taken together as an observation group. Values, given in ppm, wet weight, are shown in table 8:16.

For the evaluation of the total exposure via food, it is essential to know the consumption of different foodstuffs. In the cooperative study mentioned above (Japanese Association of Public Health, 1970b), this question was also explored in the areas studied, (Namari and Nihazama basin in Miyagi Prefecture, Usui and Yanase basin in Gumma Prefecture, Sasu and Shiine basin in Nagasaki Prefecture and Okudake basin in Ooita Prefecture). The total amount of food intake ranged from 972 g to 1586 g with an average of 1264 gram. For comparison, the average intake for farmers in Japan is given as 1218 g in 1967. The daily intake of rice varied from 267 g to 404 g, of wheat from 27 to 78 g, and of potato from 38 to 107 g. In other vegetables and mushroom, it varied from 153 to 357 g, in raw fish from 22 to 94 g, in dried fish from 24 to 59 g and in milk from 9 to 54 g.

8.4.2.2 Other areas under observation

No medical data are available but the report by the cooperative study group (Japanese Association of Public Health, 1970b), contains data on cadmium content in foodstuffs. Table 8:15 gives data for self-stored rice and bean paste. It is obvious that several of the areas under observation have considerably higher contents of cadmium in these foods than control areas. The high content of cadmium in rice from the control area in the Usui-Yanase basin is noteworthy, meaning perhaps that this area is in fact a contaminated area.

Some data on airborne cadmium exist from Annaka City district in Gumma Prefecture. The cadmium in air is considered to be due to emissions from a refinery with a capacity of 14,500 tons per month, the largest in Japan. Values from three sampling stations in the district showed 0.008-0.235 (average: 0.104), 0.044-0.380 (average: 0.166) and 0.020-0.142 (average: 0.055) $\mu g/m^3$ (Yamagata and Shigematsu, 1970).

8.5 ETIOLOGY

Clinical material has shown that the Itai-itai disease can be classified as a form of osteomalacia. Generally, osteomalacia can be divided into the following categories:

A. Vitamin D deficiency
B. Malabsorption of Vitamin D and bone minerals
C. So-called Vitamin D resistant osteomalacia

Since hyperparathyroidism sometimes shows a clinical picture similar to osteomalacia, a differential diagnosis can be very difficult. Therefore, it has also occasionally been difficult to differentiate between the Itai-itai disease and hyperparathyroidism, as discussed by Takase et al., 1967, and in a recent report on the differential diagnosis of the Itai-itai disease (Japanese Association of Public Health, 1970a). In primary hyperparathyroidism, the patients have an elevated blood calcium level not seen in cases of osteomalacia. However, a more or less decreased calcium level, seen in cases of osteomalacia, can stimulate increased parathyroid activity, so-called secondary hyperparathyroidism.

8.5.1 Vitamin D deficiency

This type of osteomalacia is dependent on the combination of lack or low intake of Vitamin D in the diet and deprivation of ultraviolet irradiation. This combination, together with a low intake of calcium, and a simultaneous high demand for calcium and Vitamin D during pregnancy and lactation have in some cases given rise to osteomalacia even in countries with much sunshine, as documented by Green et al., 1965 (see also the review by Arnstein, Frame and Frost, 1967). In the areas where the Itai-itai disease is seen, the consumption of foodstuffs rich in calcium and Vitamin D such as milk and milk products is very low. Thus, the Vitamin D and calcium intake is considerably lower than in a country such as Sweden, as seen in table 8:8. However, the consumption is not lower than in other parts of Japan where Itai-itai disease is not seen. As we have said before, the weather in this part of Japan is very gloomy, with a lot of rain and snow. The women also wear their clothes in such a manner that the main part of the sunlight is screened away. Osteomalacia and rickets have also been more frequently seen in the Toyama Prefecture than in other parts of Japan (Kajikawa et al., 1957). The dietary conditions can not explain the etiology of the disease, because conditions are similar in nearby villages and towns where the disease has not been found, but might be subsidiary factors for the elicitation of the disease.

8.5.2 Malabsorption syndrome

Osteomalacia can also be caused by a deficient absorption of Vitamin D and bone minerals. Chronic pancreatic disease, hepatobiliary disease and resection of parts of the gastrointestinal tract have given rise to such osteomalacia, as reviewed by Arnstein, Frame and Frost, 1967, Boström, 1967 and Muldowney, 1969. In this context, the clinical observations reported by Murata et al., 1970, concerning the function of the gastrointestinal tract and pancreas are of interest. In his 1970 paper Murata mentioned that he had detected a tendency toward a declined function of the pancreas in many cases. Furthermore, examinations of the gastrointestinal tract have shown shortened ciliated epithelia as well as atrophy of the mucous membrane and submucosal cell infiltration in the small intestine. Fat absorption tests have shown decreased fat absorption in many cases. These changes in the gastrointestinal tract have been called "cadmium enteropathy" by Murata. At the present, it is impossible to judge how frequent these changes are. Murata did not state information about frequency. However, in cases in which changes are present, they could act as a contributory etiological factor of the Itai-itai disease.

8.5.3 So-called Vitamin D resistant osteomalacia (renal osteomalacia)

This form of osteomalacia is caused by a renal tubular dysfunction which gives rise to losses of bone minerals, primarily phosphate, through the kidneys. Hereditary forms have been described by Dent, 1956, but a Fanconi syndrome caused by toxic substances such as heavy metals can produce the same defect. Persons with the Itai-itai disease always have proteinuria of a tubular type. There is also an increased excretion of amino acids and glucose. The osteomalacia seen in Itai-itai patients is mainly of the same nature as hereditary forms but no hereditary factor has been found.

8.5.4 Cadmium as an etiological factor

It has been well established (Chapter 6) that exposure to cadmium can give rise to tubular damage of the kidneys with proteinuria and glucosuria. The kidney damage seen in Itai-itai disease has been very similar to that seen in classical industrial chronic cadmium poisoning,,but bone changes have not been a common finding in the latter condition. There are, however, two French accounts by Nicaud, Lafitte, and Gros, 1942, and Gervais and Delpech, 1963, and two British studies by Bonnell, 1955, and Adams, Harrison and Scott, 1969, which, taken together, show that both in male and female workers occupationally exposed to cadmium, bone changes similar to those seen in Itai-itai disease have occurred (section 6.4).

Data from industrial exposure refer mostly to males, while almost all of the Itai-itai patients have been females. It should be stressed, however, that in the endemic area, the prevalence of proteinuria and glucosuria has been extremely high also in males and only slightly lower than in females. Thus, if cadmium is the cause of the disease, there is no pronounced difference in the prevalence of functional disturbances, but only in manifestations. When tubular dysfunction disturbs the metabolism of calcium and phosphorus, women will be affected more than men. This is particularly the case in the women involved who were multiparas and who lived in an area with a low intake of calcium and probably also of Vitamin D. Therefore, it is not contradictory to a cadmium etiology that almost exclusively females have suffered from bone changes.

Although no data exist concerning the cadmium exposure several years ago, when it was supposedly highest, available information on cadmium concentrations in rice and paddy fields from recent years has shown a close correlation between high cadmium concentrations and the occurrence of Itai-itai. Furthermore, an association between cadmium concentration and the prevalence of proteinuria and glucosuria has been shown in the endemic area as well as in another area, Tsushima Island. This area has been selected by the Japanese government for detailed studies on suspected cadmium intoxication.

The question remains whether or not the cadmium exposure has been high enough to cause intoxication. This question can be approached in two different ways. One can evaluate the exposure either from data on cadmium concentrations in biological material or from data on exposure via food, water and air together with estimations of absorption and excretion rates.

Data on cadmium concentrations in biological materials are available only on a limited basis. Blood and urinary values have shown an increased amount of cadmium but do not lend themselves to a quantitative evaluation of risks. However, a few data on cadmium concentrations in organs from deceased Itai-itai patients have shown values for liver and pancreas quite comparable with those found in workers with symptoms of chronic cadmium poisoning. The liver values are about 50 times higher than in people in the United States, the United Kingdom and Sweden, not occupationally exposed and also considerably higher than the average in "control groups" in Japan. Cadmium concentrations in kidney are low, in fact, somewhat lower than in the "control groups" from Japan. There is all reason to believe that these low values are consistent with a pronounced kidney damage in the Itai-itai patients as discussed earlier in this report.

As has been mentioned, exposure data from several years ago are not available. Yamagata and Shigematsu, 1970, calculated the daily intake of cadmium during recent years in the endemic area as 600 µg, making 200 mg per year.

In section 6.1.2.4 it was concluded that a critical level in renal cortex for renal tubular dysfunction could be estimated to 200 ppm (wet weight) of cadmium. In the same section it was discussed which cadmium exposure that is necessary, via the peroral route, to give rise to this kidney level under different assumptions concerning absorption rates of cadmium. Table 6:2 gives data on the necessary exposure for different exposure times as well as for assumed absorptions of 2.5, 5 and 10 percent. As can be seen in this table, 600 µg cadmium per day may cause renal dysfunction after only a few years with a 10 percent absorption of cadmium. With an assumed absorption of 5 percent it would take about 10 years and with a 2.5 percent absorption about 20 years. There could thus be no doubt that the cadmium exposure in the endemic area, even now, is quite sufficient to cause renal damage, especially as the estimations are based on a body weight of 70 kg. This weight is well above the average body weight in the endemic area. One does not have to postulate that the exposure in the past must have been higher, even if this probably has been the case, in order to explain the renal dysfunction. We do not know exactly how severe the renal damage must have been to cause osteomalacia. It seems quite clear, however, that possibilities of a very high absorption during long times have existed.

8.6 CONCLUSIONS

In conclusion, nothing essential has spoken against cadmium as the etiological environmental agent causing the Itai-itai disease. Since in fact, all available data strongly support a hypothesis that cadmium is the cause, we have no doubts that the Itai-itai disease is a manifestation of chronic cadmium poisoning. It might well be, however, that cadmium has acted upon a population particularly sensitive because of deficient consumption of certain essential food ingredients and vitamins. A low intake of calcium and Vitamin D may have been of particular importance.

It should be emphasized that the Itai-itai disease is only one manifestation of chronic cadmium poisoning. The high prevalence of proteinuria and glucosuria without bone changes in the endemic area certainly is a manifestation of chronic cadmium poisoning. There is every reason to believe that cadmium intoxication has occurred in other parts of Japan than the Toyama Prefecture. Data from the Tsushima Island strongly support such a hypothesis. It is impossible to estimate quantitatively the extent of the cadmium problem in Japan solely on the basis of available data. Because cadmium is used extensively in industry, in mining and smelting operations which are common in Japan, the cadmium problem may well be far-reaching. Only additional epidemiological studies in potentially exposed areas can elucidate that question.

Table 8:1 NUMBER OF PATIENTS AND SUSPECTED. Results of 1962-1965 epidemiological research. Women over 40 years of age. Also men over 40 years of age in Tonami City (from Ishizaki and Fukushima, 1968).

District	Number examined	[x]Number of patients and suspected		
		I(I)	i	(i)
[xx]Kumano, Fuchumachi	259	9	8	13
[xx]Others "	9	2	0	1
[xx]Shinbo, Toyama City	352	15	5	3
Osawano-cho	411	2	1	2
Ota, Toyama City	334	0	0	0
Nyuzen-cho	1180	0	0	0
Tonami City	1100	0	0	0

[x] Decided mainly by X-ray

[xx] Jintsu River basin

I:	Patient (typical bone signs on X-ray)
(I):	Person cured of Itai-itai disease
i:	Deeply suspected (bone signs but not typical)
(i):	Suspected (bone signs, slight)

Table 8:2 QUESTIONNAIRE FOR FIRST SCREENING PROCEDURE IN THE 1967 EPIDEMIOLOGICAL STUDY (from Kato and Kono, 1968).

Please answer all of the following questions. Try to overcome any difficulties you might have in recalling the answers, "yes" or "no".

		Yes	No
1.	Have you ever been told that you are an Itai-itai patient?	____	____
2.	Have you ever suffered from neuralgia or rheumatism?	____	____
3.	Have you ever suffered from a bone or joint disease?	____	____
4.	Have you ever suffered from a low back pain?	____	____
5.	Have you ever suffered from a kidney disease?	____	____
6.	Have you ever suffered from diabetes?	____	____
7.	Do you have a low back pain now?	____	____
8.	Do you have an arm, leg, or foot pain now?	____	____
9.	Do you have a joint pain now?	____	____
10.	Do you have neuralgia now?	____	____
11.	Have you difficulty walking now?	____	____
12.	Have any of your family members (father, mother, brother, sister, husband, wife, or children) died of Itai-itai disease?	____	____
13.	Have any of your family members died of kidney diesase?	____	____
14.	Have any of your family members died of diabetes?	____	____
15.	Have any of your family members suffered from rickets?	____	____

Table 8:3 RESULTS FROM 1967 FINAL EXAMINATION (from Ishizaki and Fukushima, 1968).

		Total	I	i	(i)	0_{ob}	0
	Total	419	50	17	31	136	185
District	Fuchumachi	227	28	11	14	79	95
	Toyama City	105	16	3	8	34	44
	Osawano-cho	53	6	3	6	16	22
	Yao-cho	34	-	-	3	7	24
Sex	♂	122	1	1	3	37	80
	♀	297	49	16	28	99	105
Age	30-44	39	-	-	-	2	37
	45-59	86	6	-	2	28	50
	60-74	225	40	10	22	86	67
	75 +	69	4	7	7	20	31
	Mean age:		66.6	72.2	68.3	66.1	58.0

I: Patient (typical bone signs on X-ray)
i: Deeply suspected (bone signs but not typical)
(i): Suspected (bone signs, slight)
0_{ob}: Need for continuous observation (urinary and/or blood signs)
0: No suspicion

Table 8:4 NUMBER OF ITAI-ITAI PATIENTS REGISTERED BY TOYAMA PREFECTURE HEALTH AUTHORITIES, SEPT. 1968 (from Kubota et al., 1969).

	[x]I		i		(i)		O_{ob}		Total		
Age	Male	Fem.	M	F	M	F	M	F	M	F	Total
30-39											
40-49		2				1		2		5	5
50-59		6		2			3	14	3	22	25
60-69		31		14		5	12	40	12	90	102
70-79		12		5		6	14	30	14	53	67
80-89		2	1	6		1	3	5	4	14	18
Total		53	1	27		13	32	91	33	184	217

[x] For explanation of symbols for the Itai-itai classification, see table 8:3.

Table 8:5 NUMBER OF PATIENTS WITH ITAI-ITAI DISEASE ACCORDING TO YEAR OF ONSET OF DISEASE ESTIMATED BY PATIENTS' COMPLAINTS (patients registered by Toyama Prefecture, June 15, 1968)

(from Kato and Kono, 1968).

Total		Starting year					
		Before 1934	1935-1944	1945-1954	1955-1964	1965-later	not clear
Total	92	6	10	25	33	12	6
[x]I	51	4	7	16	16	5	3
i+(i)	41	2	3	9	17	7	3

[x] For explanation of symbols for the Itai-itai classification, see table 8:3.

Table 8:6 NUMBER OF PERSONS EXAMINED FOR PROTEINURIA AND GLUCOSURIA, Men and women in different districts and in different age groups at the 1967 epidemiological study (Ishizaki, personal communication).

	Men						Women					
Age group	30-39	40-49	50-59	60-69	70-	Total	30-39	40-49	50-59	60-69	70-	Total
Endemic district	394	382	291	255	160	1482	503	392	352	289	134	1670
Borderline district	97	95	73	66	32	363	109	99	95	78	47	428
Non-endemic district	306	220	202	178	85	991	349	245	265	184	116	1159
Total	797	697	566	499	277	2836	961	736	712	551	297	3257

Table 8:7 PREVALENCE OF PROTEINURIA AND NUMBER EXAMINED (1960-1962). MEN AND WOMEN OF DIFFERENT AGES IN HIROSHIMA AND NAGASAKI (from Freedman et al., 1967).

	Male		Female	
Age at examination (years)	Number tested	Positive tests (percent)	Number tested	Positive tests (percent)
		Hiroshima		
10-19	118	6.8	163	3.1
20-29	329	2.4	524	4.4
30-39	708	2.8	1,576	2.5
40-49	501	3.6	1,085	3.5
50-59	678	7.1	1,245	7.2
60-69	616	11.4	837	8.8
70 +	219	19.2	275	24.0
Total	3,169	6.8	5,705	5.9
		Nagasaki		
10-19	60	3.3	62	1.6
20-29	188	1.6	273	1.1
30-39	321	1.6	769	1.4
40-49	211	3.3	294	3.1
50-59	233	3.4	234	4.3
60-69	174	3.4	134	2.2
70 +	33	12.1	47	10.6
Total	1,220	2.9	1,813	2.3

Table 8:8 NUTRITIONAL DATA FROM JAPAN AND SWEDEN
(Japanese data for 1955 and 1956 from Takase et al., 1967, or Tsuchiya, 1969; Swedish data for 1960 from Blix et al., 1965).

Foodstuff		Itai-itai Patients' Homes[x]	Kumano District[x]	Mean in Rural District (Toyama Pref.)	Mean in Japan	Mean in Sweden
Calorie	(cal)	2,139	2,209	2,237	2,074	2,868
Protein	(g)	73	74	62	69	74
Fat	(g)	14	17	17	21	124
Ca	(mg)	408	374	331	364	938
P	(mg)	1,556	1,432	1,433	1,822	1,378
Fe	(mg)	34	15	23	6	14
Vit. A	(I.U.)	1,325	1,754	1,376	2,814	3,267
Vit. B_1	(mg)	0.8	1.1	1.0	1.1	1.8
Vit. B_2	(mg)	0.6	0.6	0.7	0.7	1.8
Vit. C	(mg)	69	93	64	66	75
Vit. D	(mg)					5.1

[x] Total: 200 households

Table 8:9 SOCIO-ECONOMIC DATA CONCERNING ITAI-ITAI PATIENTS AND CONTROLS (Ishizaki, personal communication).

Factors studied	Itai-itai Patients (124 women, 3 men, mean age:67.6)	Controls (124 women, 3 men, mean age:66.3)
	Percent	Percent
1. Lived in same area 40 years or more	96	77[x]
2. Worked in agriculture	83	79
3. Six or more pregnancies	56	41[x]
4. Drank water from Jintsu River	83	57[x]
5. Total family income 1,000,000 yen or more	15	28[x]
6. "Better" condition of living room	61	63
7. Refrigerator in house	56	64
8. Area of rice field (mean)	1 hectar	1 hectar

[x] Difference statistically significant

Table 8:10 CADMIUM CONTENT (ppm, wet weight) IN ORGANS FROM FEMALE ITAI-ITAI PATIENTS (from Ishizaki, Fukushima, and Sakamoto, 1970b).

Organ	Patient 1 age: 79	Patient 2 age: 71	Patient 3 age: 60	Patient 4 age: 73
Liver	94.1	118.1	63.3	89.0
Renal cortex	41.1	31.8	19.8^{x}	
Renal medulla	39.5	26.1		
Lung		2.5	8.0	
Spleen		6.8	6.2	
Pancreas	45.1	64.7		
Stomach				4.8
Small intestine		3.0	12.5	5.7
Large intestine		1.7	11.9	
Ribs			2.8	
Bone cortex		1.6		
Bone marrow		1.1		
Skin		4.6	5.1	3.9
Muscles		14.1		
Brain	0.6			

^{x}Cortex and medulla not separated

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	Percent	Percent
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2. Worked in agriculture	83	79
3. Six or more pregnancies	56	41^x
4. Drank water from Jintsu River	83	57^x
5. Total family income 1,000,000 yen or more	15	28^x
6. "Better" condition of living room	61	63
7. Refrigerator in house	56	64
8. Area of rice field (mean)	1 hectar	1 hectar

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Liver	94.1	118.1	63.3	89.0
Renal cortex	41.1	31.8	19.8[x]	
Renal medulla	39.5	26.1		
Lung		2.5	8.0	
Spleen		6.8	6.2	
Pancreas	45.1	64.7		
Stomach				4.8
Small intestine		3.0	12.5	5.7
Large intestine		1.7	11.9	
Ribs			2.8	
Bone cortex		1.6		
Bone marrow		1.1		
Skin		4.6	5.1	3.9
Muscles		14.1		
Brain	0.6			

[x] Cortex and medulla not separated

Table 8:11 NUMBER AT RISK, NUMBER EXAMINED AND PERCENTAGE EXAMINED IN DIFFERENT AREAS OF TSUSHIMA ISLAND IN MALES AND FEMALES IN DIFFERENT AGE GROUPS (from Department of Health, Nagasaki Prefecture, 1970)

	Sex	Male					Female					
Village	Age	40-49	50-59	60-69	70-	Total	40-49	50-59	60-69	70-	Total	Total
Hikage-Kamiyama	Number at Risk	24	11	13	2	50	28	12	11	7	58	108
	Number Examined	14	8	8	1	31	25	10	10	3	48	79
	Percentage Examined	58.3	72.7	61.5	50.0	62.0	89.4	83.3	90.9	42.9	82.8	73.1
Shimobaru	Number at Risk	42	24	10	9	85	46	17	14	12	89	174
	Number Examined	29	15	6	2	52	33	7	5	3	48	100
	Percentage Examined	69.1	62.5	60.0	22.0	61.2	71.7	41.2	35.7	25.0	53.9	57.5
Komoda	Number at Risk	27	20	17	17	81	35	22	17	15	89	170
	Number Examined	17	14	10	9	50	27	17	12	7	63	113
	Percentage Examined	63.0	70.0	58.8	52.9	61.7	77.1	77.3	70.6	46.7	70.8	66.5
Shiine	Number at Risk	23	15	10	8	56	17	24	7	12	60	116
	Number Examined	12	12	9	5	38	15	24	6	12	57	95
	Percentage Examined	50.2	80.0	90.0	62.5	67.9	88.2	100.0	85.6	100.0	95.0	81.9
Kashine	Number at Risk	21	12	7	3	43	22	6	8	6	42	85
	Number Examined	18	10	6	2	36	21	6	8	5	40	76
	Percentage Examined	85.7	83.3	85.6	66.7	83.7	95.5	100.0	100.0	83.3	95.2	89.4
Total of Area under Observation	Number at Risk	137	82	57	39	315	148	81	57	52	338	653
	Number Examined	90	59	39	19	207	121	64	41	30	256	463
	Percentage Examined	65.7	72.0	68.4	48.7	65.7	81.8	79.0	71.9	57.7	75.7	70.9
Are Total of Control Area	Number at Risk	31	14	22	8	75	37	26	25	13	101	176
	Number Examined	5	2	6	2	15	25	17	16	5	63	78
	Percentage Examined	16.1	14.3	27.3	25.0	20.0	67.6	65.4	64.0	38.5	62.4	44.3
Total	Number at Risk	168	96	79	47	390	185	107	82	65	439	829
	Number Examined	95	61	45	21	222	146	81	57	35	319	541
	Percentage Examined	56.5	63.5	57.1	44.7	56.9	78.9	76.4	69.5	53.8	72.7	65.3

Table 8:12 PREVALENCE OF PROTEINURIA AND GLUCOSURIA

(from Department of Health, Nagasaki Prefecture, 1970).

Area	Males				Females			
	Number Examined	Percent with Proteinuria	Percent with Glucosuria	Percent with Proteinuria and/or Glucosuria	Number Examined	Percent with Proteinuria	Percent with Glucosuria	Percent with Proteinuria and/or Glucosuria
Kashine, Shiine	73	14	12	23	96	14	10	17
Shimobaru, Komoda	99	3	3	6	101	5	4	7
Hikage-Kamiyama, Are	46	0	4	4	107	6	0	6

Table 8:13 AGE DISTRIBUTION OF EXAMINED SUBJECTS (actual numbers) IN DIFFERENT AREAS (from Department of Health, Nagasaki Prefecture, 1970).

Area		Males				Females			
	Age:	40-49	50-59	60-69	70-	40-49	50-59	60-69	70-
Kashine, Shiine		30	22	15	7	36	30	14	17
Shimobaru, Komoda		46	29	16	11	60	24	17	10
Hikage-Kamiyama, Are		19	10	14	3	50	27	26	8

Table 8:14 PREVALENCE OF PROTEINURIA AND GLUCOSURIA IN FARMERS (from Department of Health, Nagasaki Prefecture, 1970).

Area	Males				Females			
	Number Examined	Percent with Proteinuria	Percent with Glucosuria	Percent with Proteinuria and/or Glucosuria	Number Examined	Percent with Proteinuria	Percent with Glucosuria	Percent with Proteinuria and/or Glucosuria
Kashine, Shiine	30	20	20	33	65	18	12	23
Shimobaru, Komoda	29	10	3	10	47	4	4	4
Hikage-Kamiyama, Are	23	0	0	0	71	6	0	6

Table 8:15 CONTENT OF CADMIUM IN SELF-STORED RICE (ppm dry weight) AND BEAN PASTE (ppm wet weight) IN DIFFERENT AREAS UNDER OBSERVATION (from Japanese Association of Public Health, 1970b).

	Rice		Bean paste	
	Average	Range	Average	Range
Sasu-Shiine basin				
Areas under observation	0.37	0.03-1.02	0.27	0.07-0.56
Kashine	0.52	0.05-1.02	0.32	0.15-0.56
Shiine-Shimobaru	0.30	0.03-0.49	0.22	0.07-0.31
Komoda	0.24	0.06-0.58	0.30	0.27-0.34
Hikage and Kamiyama	-	-	-	-
Control area (Are)	0.08	0.02-0.15	0.04	0.01-0.05
Namari-Nihazama basin				
Areas under observation	0.30	0.09-0.84	0.06	-
Control area	0.11	0.07-0.17	0.05	-
Usui-Yanase basin				
Areas under observation	-	-	-	-
Iwai	0.60	0.39-0.84	0.32	0.11-0.45
Yaden	0.30	-	0.26	0.17-0.40
Nakajuku	0.30	-	0.14	-
Itabi	0.30	-	0.16	-
Control area	0.30	-	0.13	-
Okudake basin				
Areas under observation	0.20	0.03-0.46	0.07	0.00-0.40
Sanchi-Tsudome	0.32	0.15-0.46	0.16	0.04-0.40
Miyatsum-Udae	0.23	0.03-0.37	0.03	0.00-0.06
Uda	0.05	0.03-0.07	0.02	0.00-0.04
Control area	0.03	0.01-0.05	0.01	-

Table 8:16 MEAN CONCENTRATION OF CADMIUM IN FOODSTUFFS[x]
(ppm, wet weight)
(from Department of Health, Nagasaki Prefecture, 1970).

Foodstuff	Control area (Are)	Observation area (Kashine, Shiine, Shimobaru, Komoda, Hikage-Kamiyama)
Tomato	<0.05	0.05
Watermelon	0.1	0.1
Onion	0.1	0.15
Eggplant	0.1	0.3
Mushroom	0.1	0.37
Pumpkin	<0.05	0.16
Carrot	0.15	0.44
Spinach	0.4	0.85
Potato	0.08	0.14
Taro	0.1	0.7

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[x] Note that the values are based only on very few observations (generally less than 5).

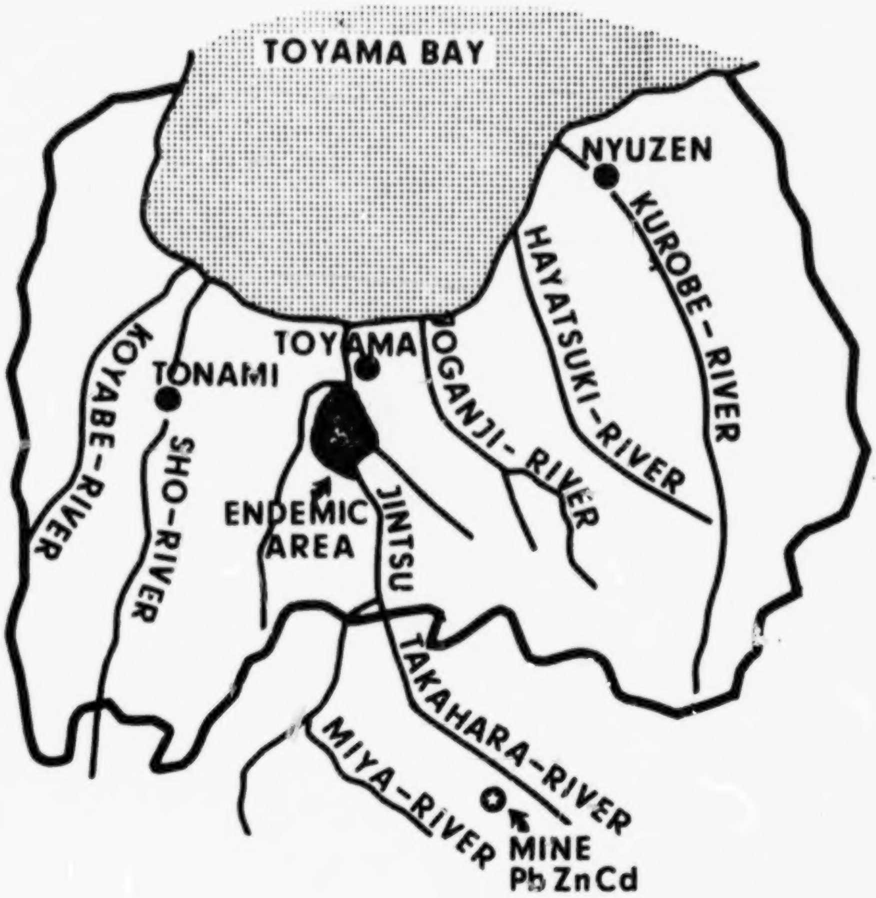

TOYAMA BAY
NYUZEN
KUROBE-RIVER
HAYATSUKI-RIVER
JOGANJI-RIVER
TOYAMA
TONAMI
KOYABE-RIVER
SHO-RIVER
ENDEMIC AREA
JINTSU
TAKAHARA-RIVER
MIYA-RIVER
MINE
Pb Zn Cd

Figure 8:1 Location of Population Centers within Toyama Prefecture, with the location of the Kamioka mine (from Ishizaki and Fukushima, 1968).

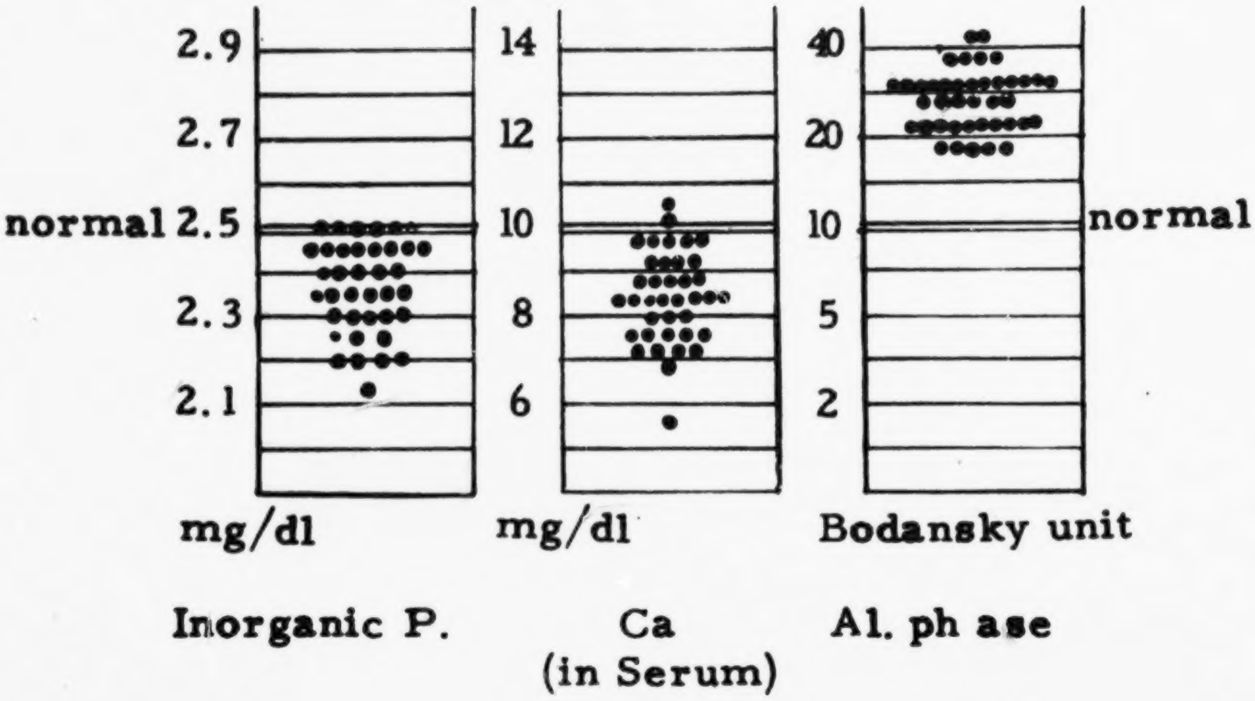
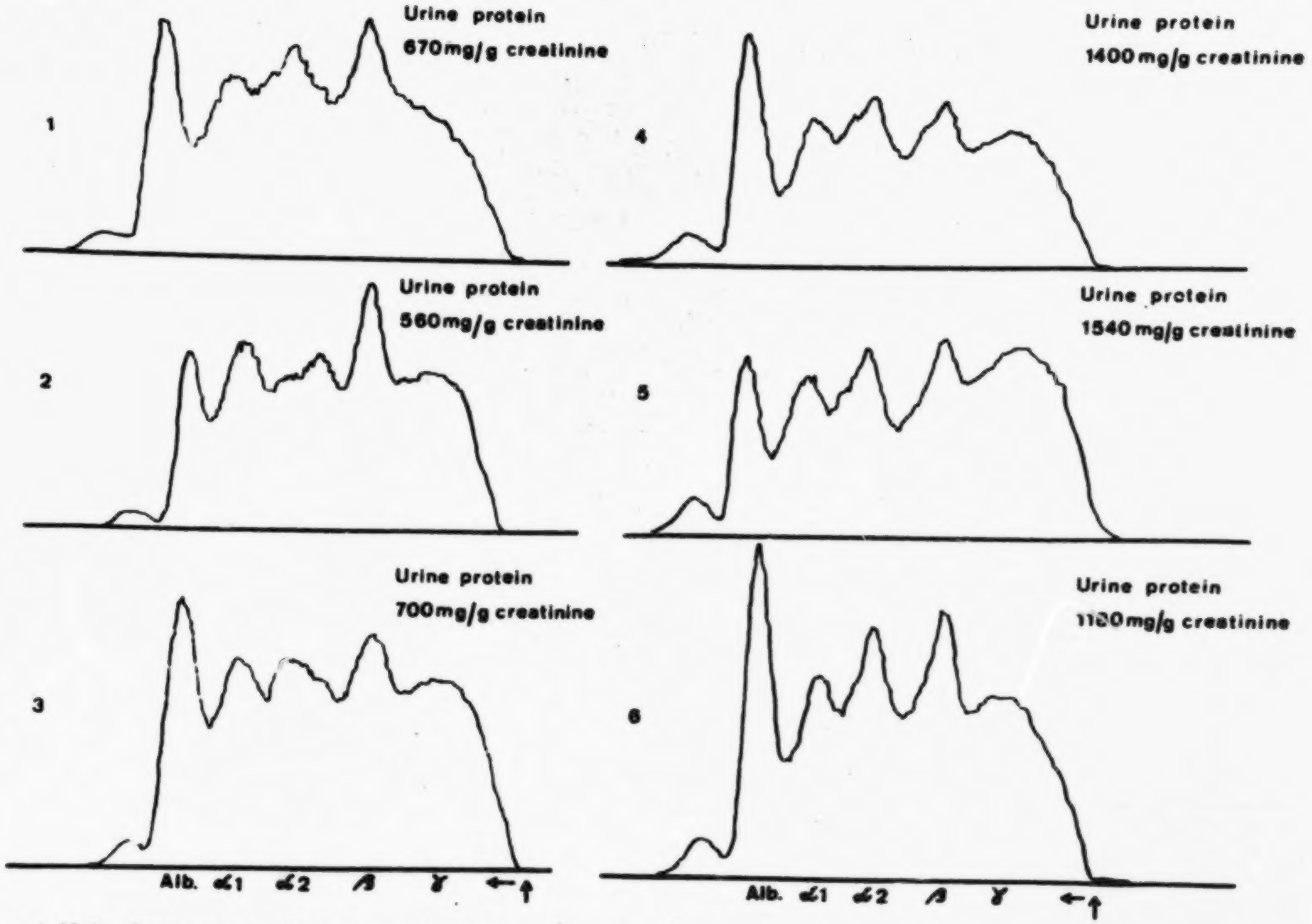


Figure 8:2 Inorganic Phosphorus, Calcium and Alkaline Phosphatase in Serum of Patients with Itai-itai Disease (from Murata et al., 1970).



1 Male Japanese worker occupationally exposed to cadmium oxide fumes.

2 and 3 Men from the endemic district with proteinuria and glucosuria without bone changes.

4 and 5. Women with Itai-itai disease.

6. Women from the endemic district with proteinuria and glucosuria without bone changes.

Figure 8:3 Electrophoretic Patterns in an Occupationally Exposed Male Japanese Worker and Male and Female Patients from the Endemic District (from Piscator and Tsuchiya, unpublished data).

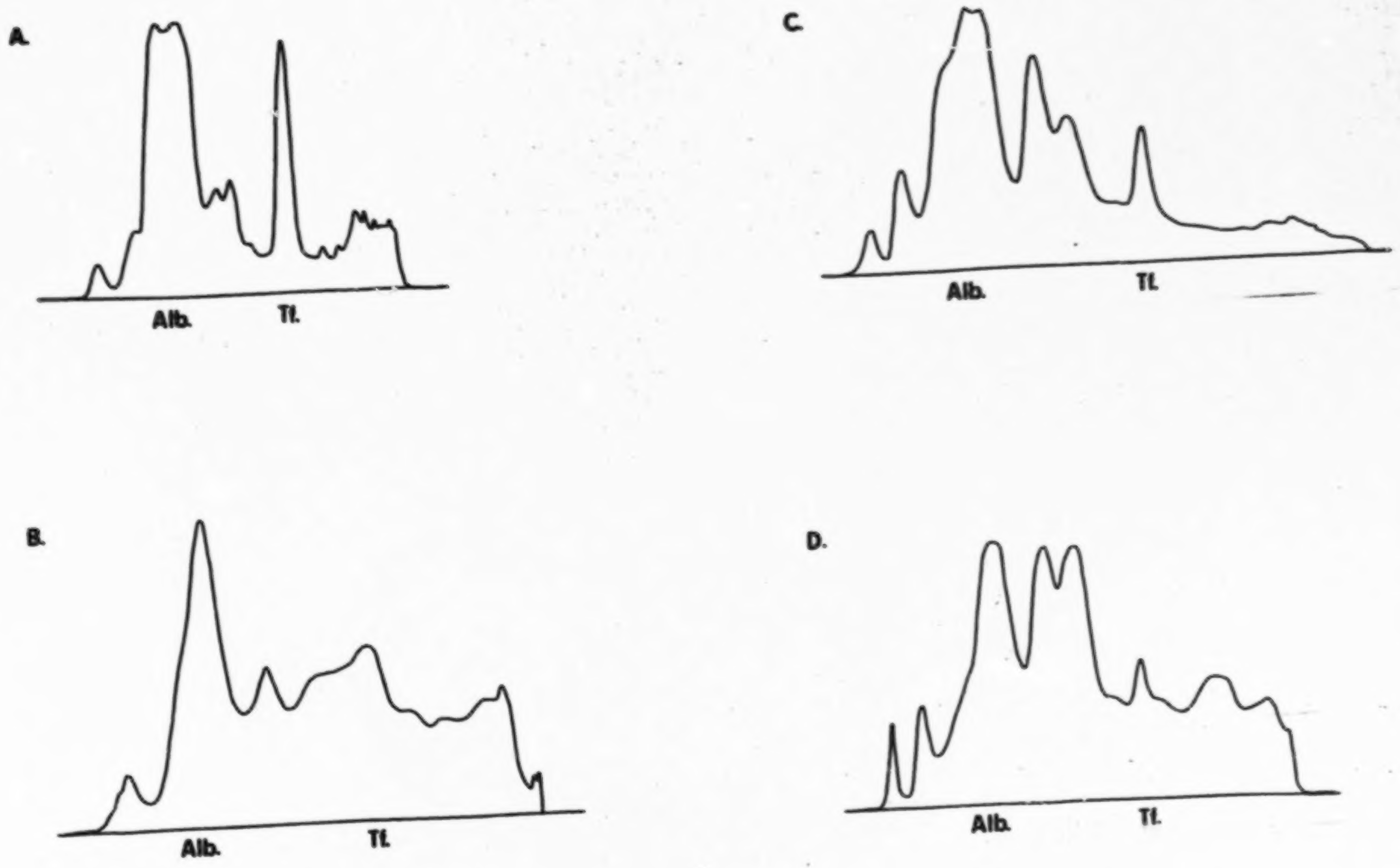
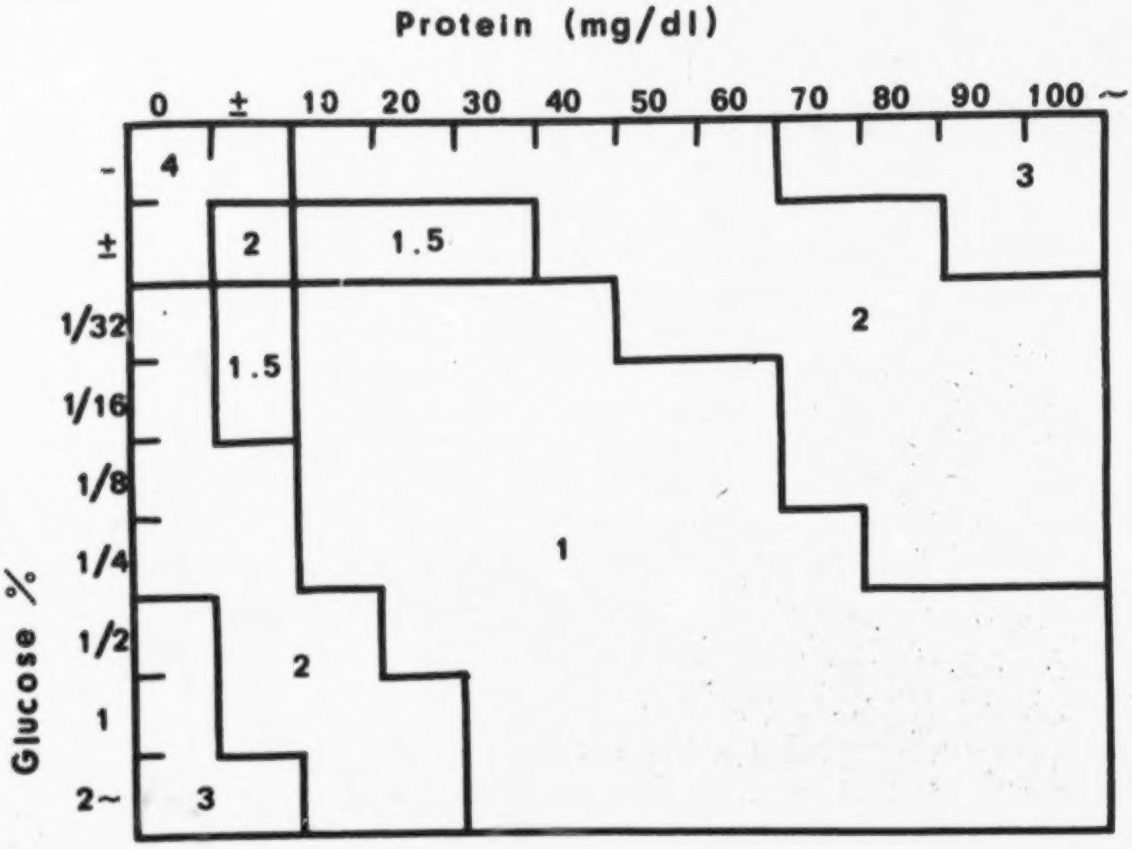


Figure 8:4 Disc-electrophoretic Patterns of Urinary Proteins from A) 19 Year-old Man with Nephrotic Syndrome, B) 22 Year-old Cadmium Exposed Worker, C) 67 Year-old Woman with Itai-itai Disease, D) 74 Year-old Woman with Proteinuria and Glucosuria, but without Bone Disease, Living in the Endemic Area for the Itai-itai Disease (from Piscator and Tsuchiya, unpublished data).

A. Screening rank from urine analysis



B. Screening rank from questionnaire

Question	total 15
on past illness	6
on subjective symptoms	5
on family	4

Number of "yes"	Rank
over 10	1
6 - 9	2
1 - 5	3
0	4

1. The subject who has an anamnesis of IId ⟶ to third exam.
2. The subject whose rank is 1 in either A or B ⟶ to second exam.
3. The subject whose rank number in total A + B is less than 5 ⟶ to second.

Figure 8:5 Selection of Subjects for the Second Examination from the Results of Urine Analysis and Questionnaire (from Kato and Kono, 1968).

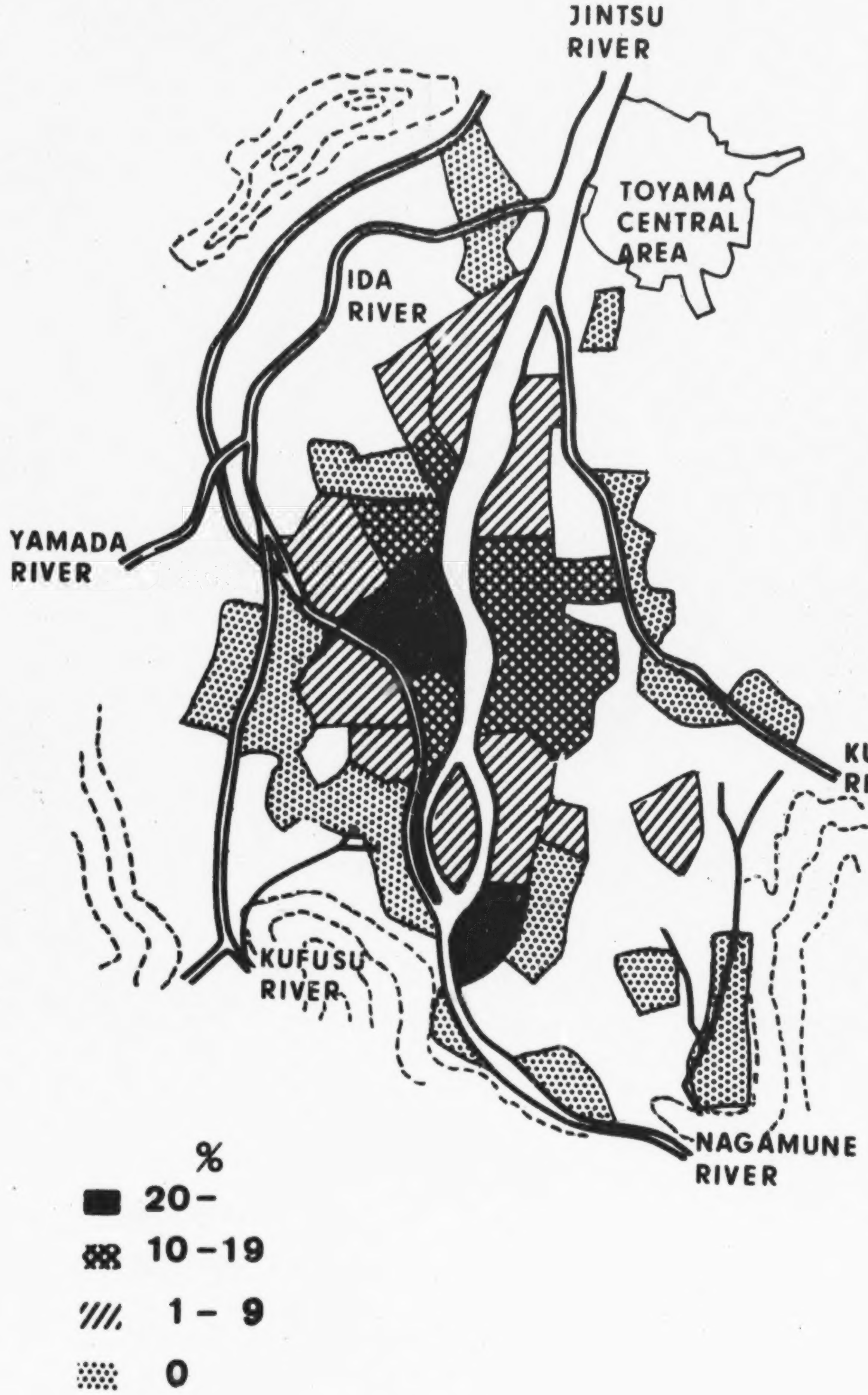

JINTSU RIVER
TOYAMA CENTRAL AREA
IDA RIVER
YAMADA RIVER
KUMANO RIVER
KUFUSU RIVER
NAGAMUNE RIVER
%
■ 20-
▩ 10-19
▨ 1- 9
░ 0

Figure 8:6 Percentage of Women over 50 Years of Age with Itai-itai Disease (I, i, or (i)) at the Examination of 1967 (from Ishizaki and Fukushima, 1968, Kato and Kono, 1968, or Yamagata and Shigematsu, 1970).

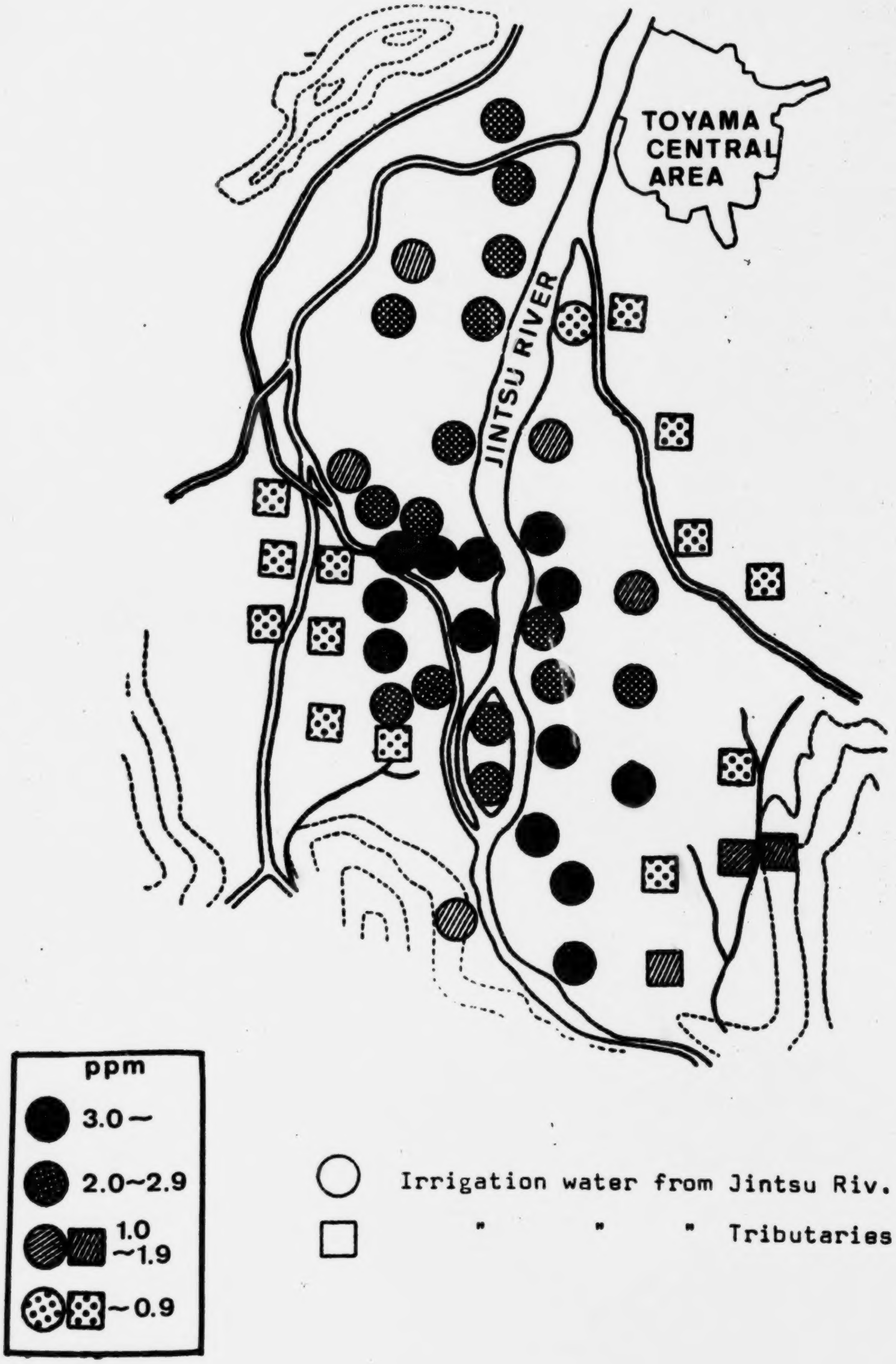

TOYAMA CENTRAL AREA
JINTSU RIVER
ppm
3.0~
2.0~2.9
1.0 ~1.9
~0.9
○ Irrigation water from Jintsu Riv.
□ " " " Tributaries

Figure 8:7 Distribution of Cd in Paddy Soil, Surface Layer (from Kato and Kono, 1968, or Yamagata and Shigematsu, 1970).

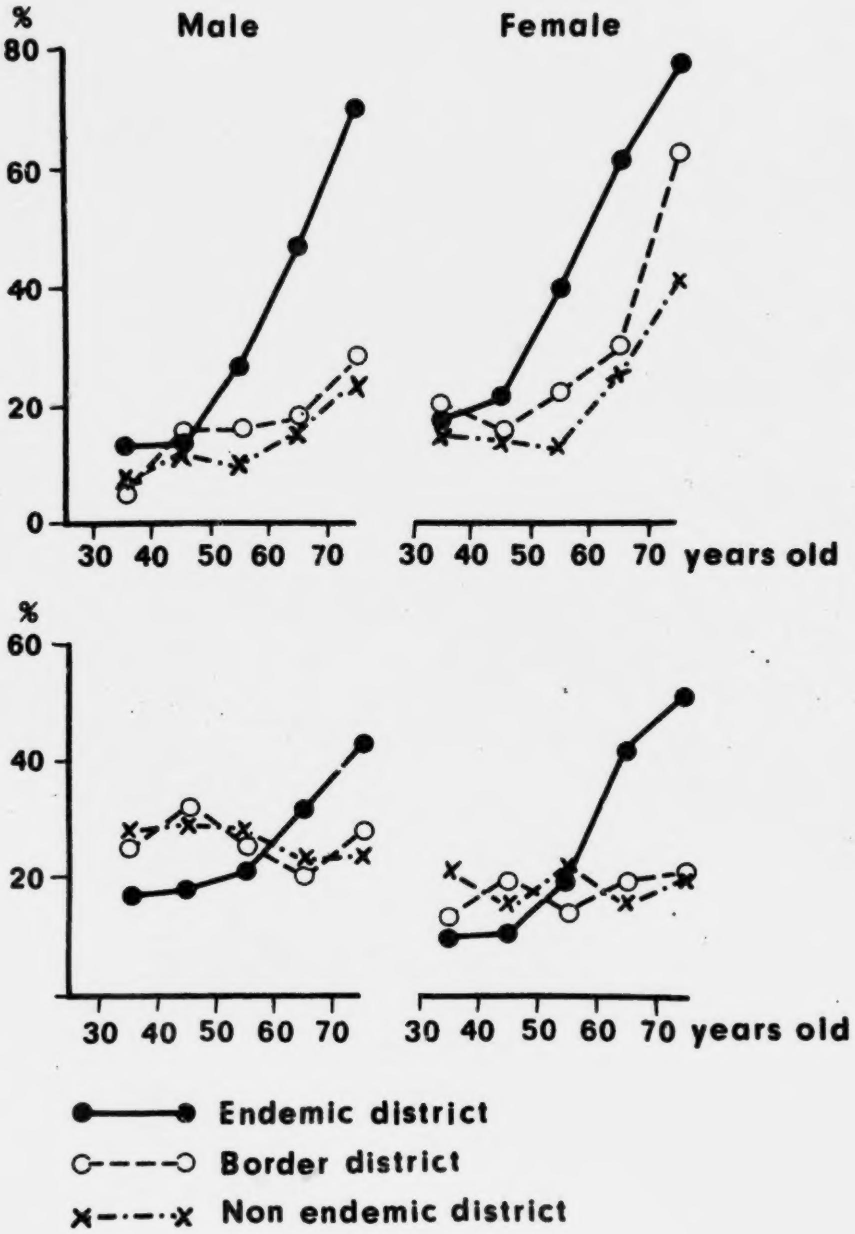


Figure 8:8 Prevalence of Proteinuria (above) and Glucosuria (below) in Different Districts in Men and Women in Different Age Groups at the 1967 Epidemiological Study (from Ishizaki, 1969b).

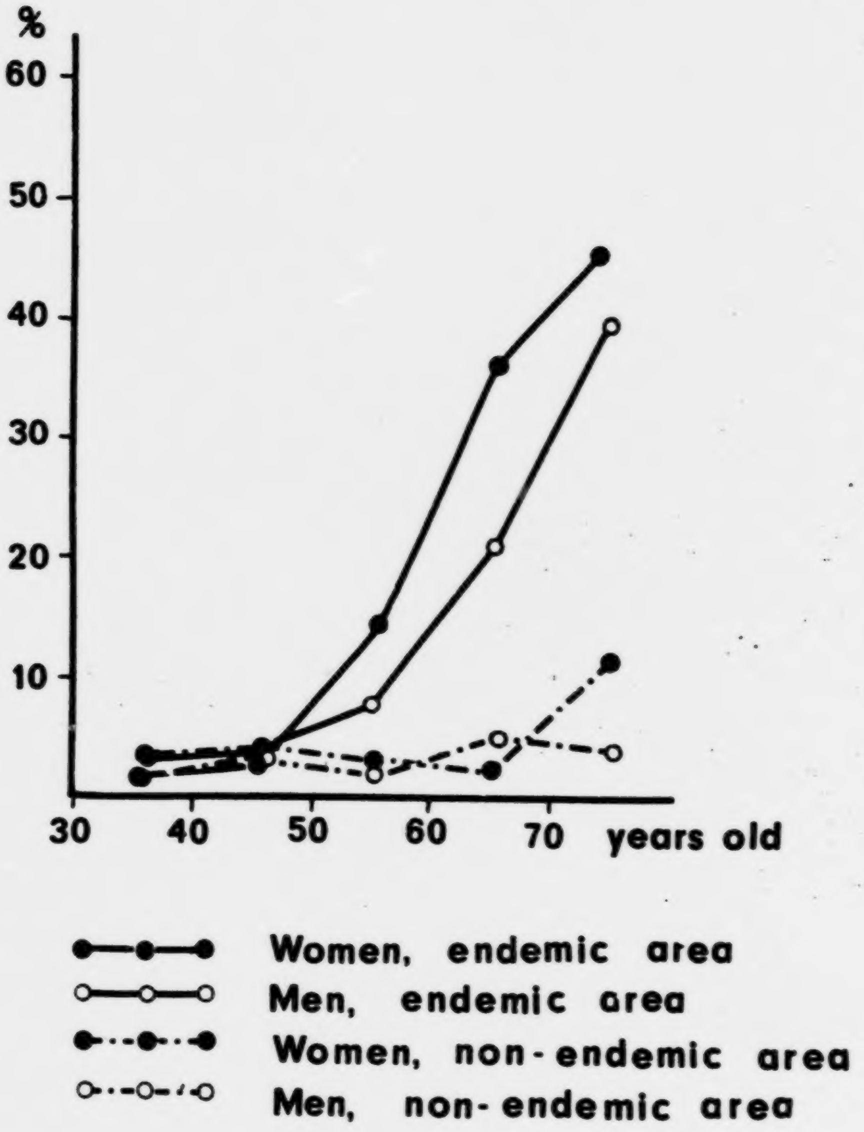


Figure 8:9 Concurrent Prevalence of Proteinuria and Glucosuria in Endemic and Non-endemic Districts in Men and Women in Different Age Groups at the 1967 Epidemiological Study (modified from Ishizaki, 1969b).

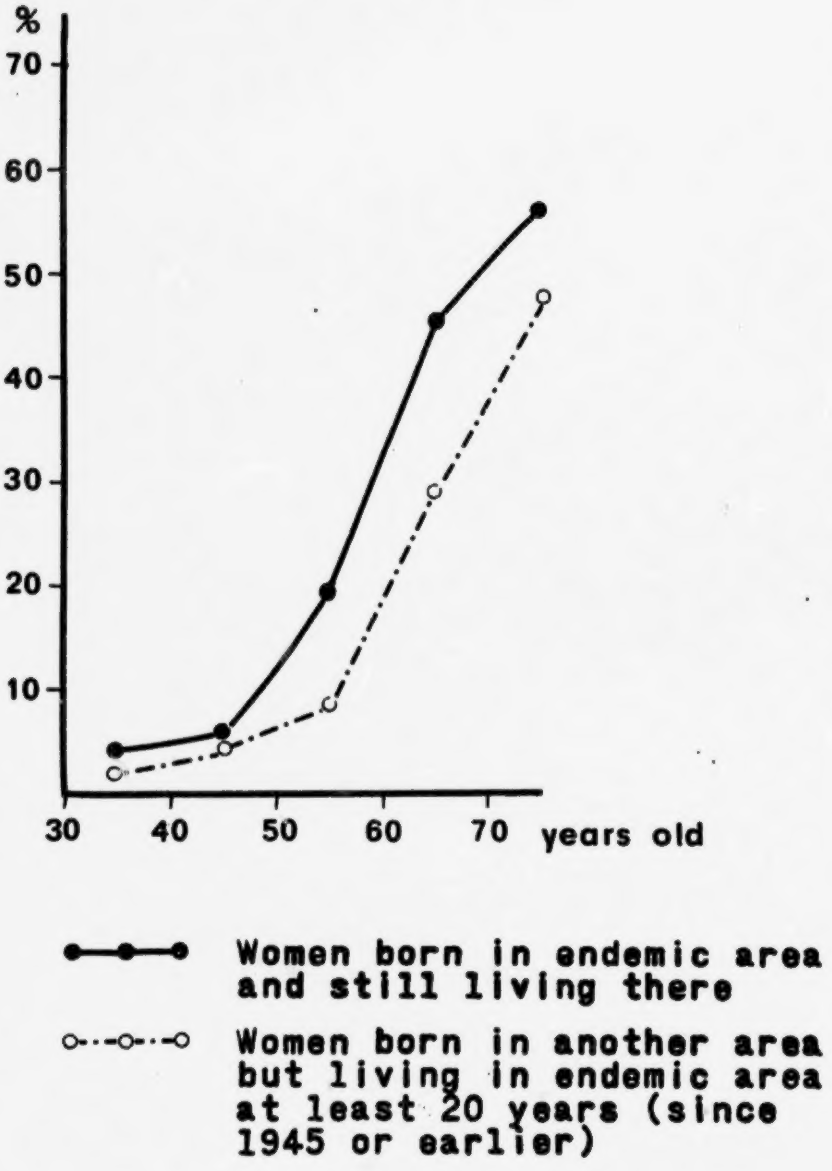


Figure 8:10 Concurrent Prevalence of Proteinuria and Glucosuria in Women in Different Age Groups in the Endemic District According to Place Born (Fukushima, personal communication).

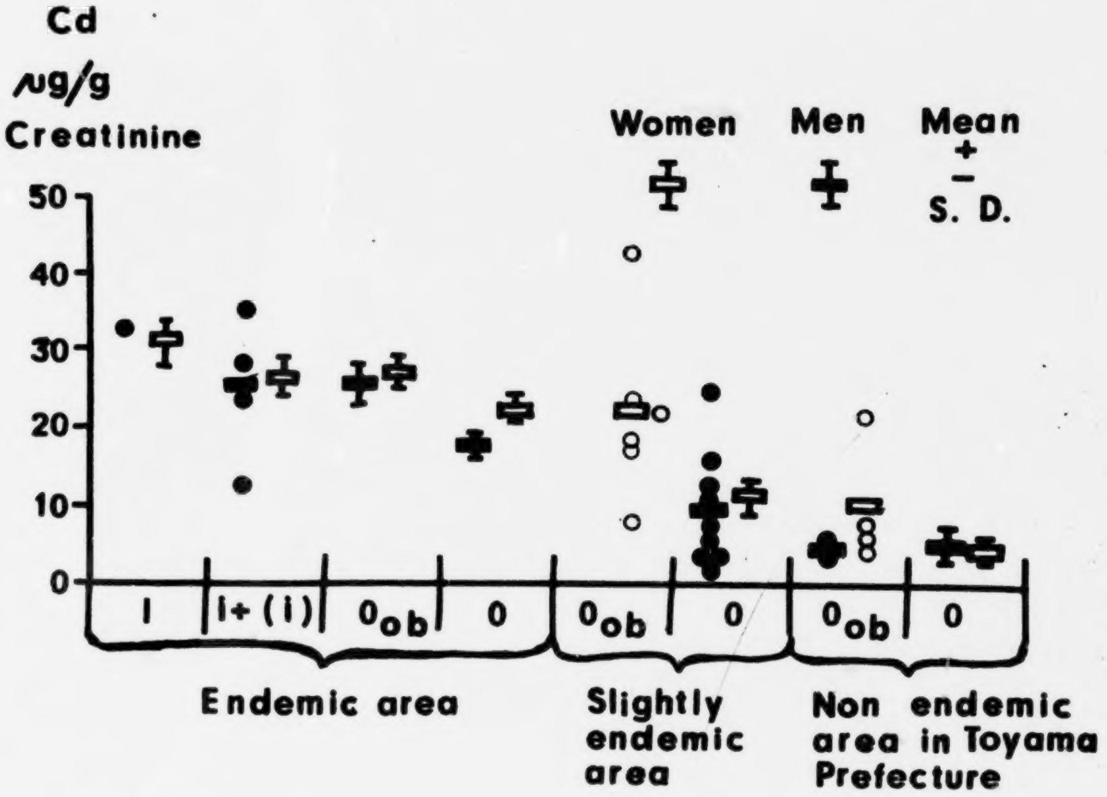


Figure 8:11 Cadmium Concentration in Urine of Persons from Different Areas in Toyama Prefecture (from Ishizaki, 1969b).

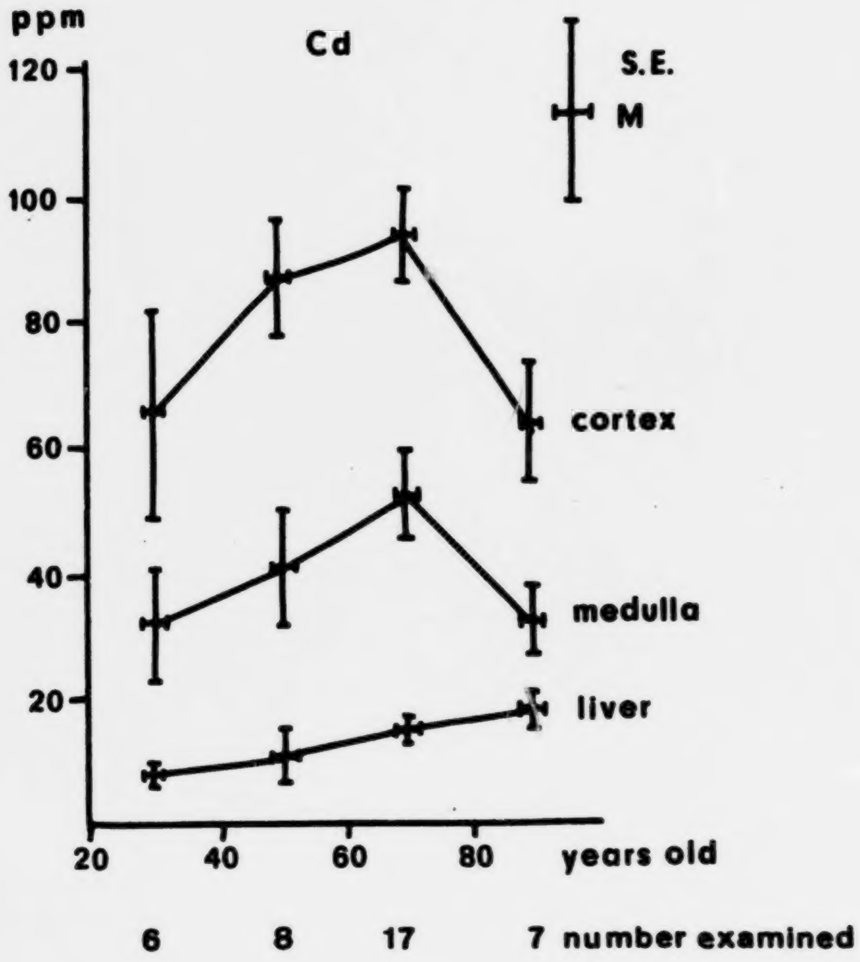


Figure 8:12 Cadmium Content (ppm wet weight) in Controls who died in hospitals in Kanazawa (from Ishizaki, Fukushima, and Sakamoto, 1970b).

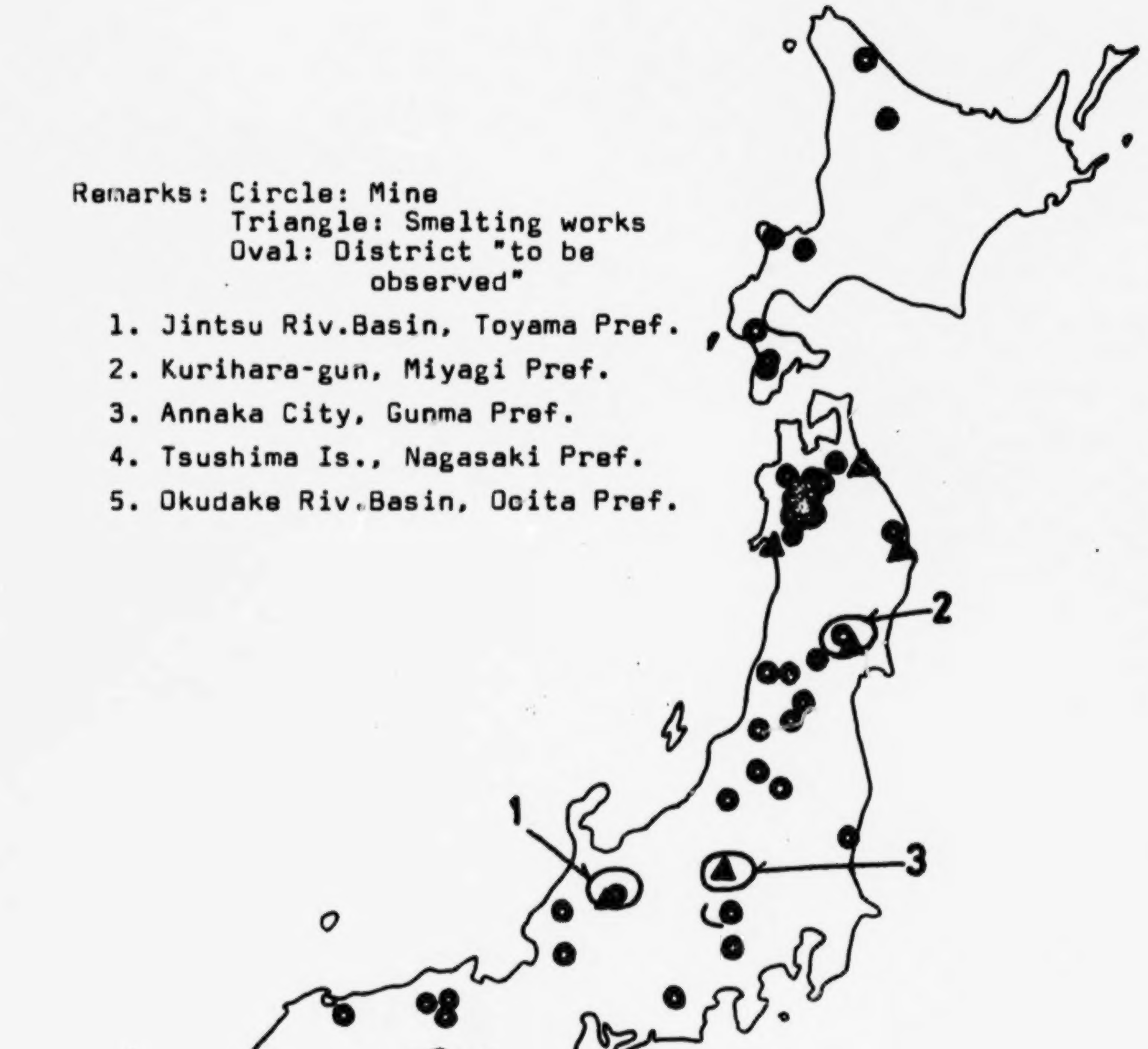

Remarks: Circle: Mine
Triangle: Smelting works
Oval: District "to be observed"
1. Jintsu Riv.Basin, Toyama Pref.
2. Kurihara-gun, Miyagi Pref.
3. Annaka City, Gunma Pref.
4. Tsushima Is., Nagasaki Pref.
5. Okudake Riv.Basin, Ooita Pref.
1
2
3
4
5

Figure 6:13 Distribution of Sulphide Ores (Cu, Pb, Zn) and Smelting Works in Japan (from Yamagata and Shigematsu, 1970).

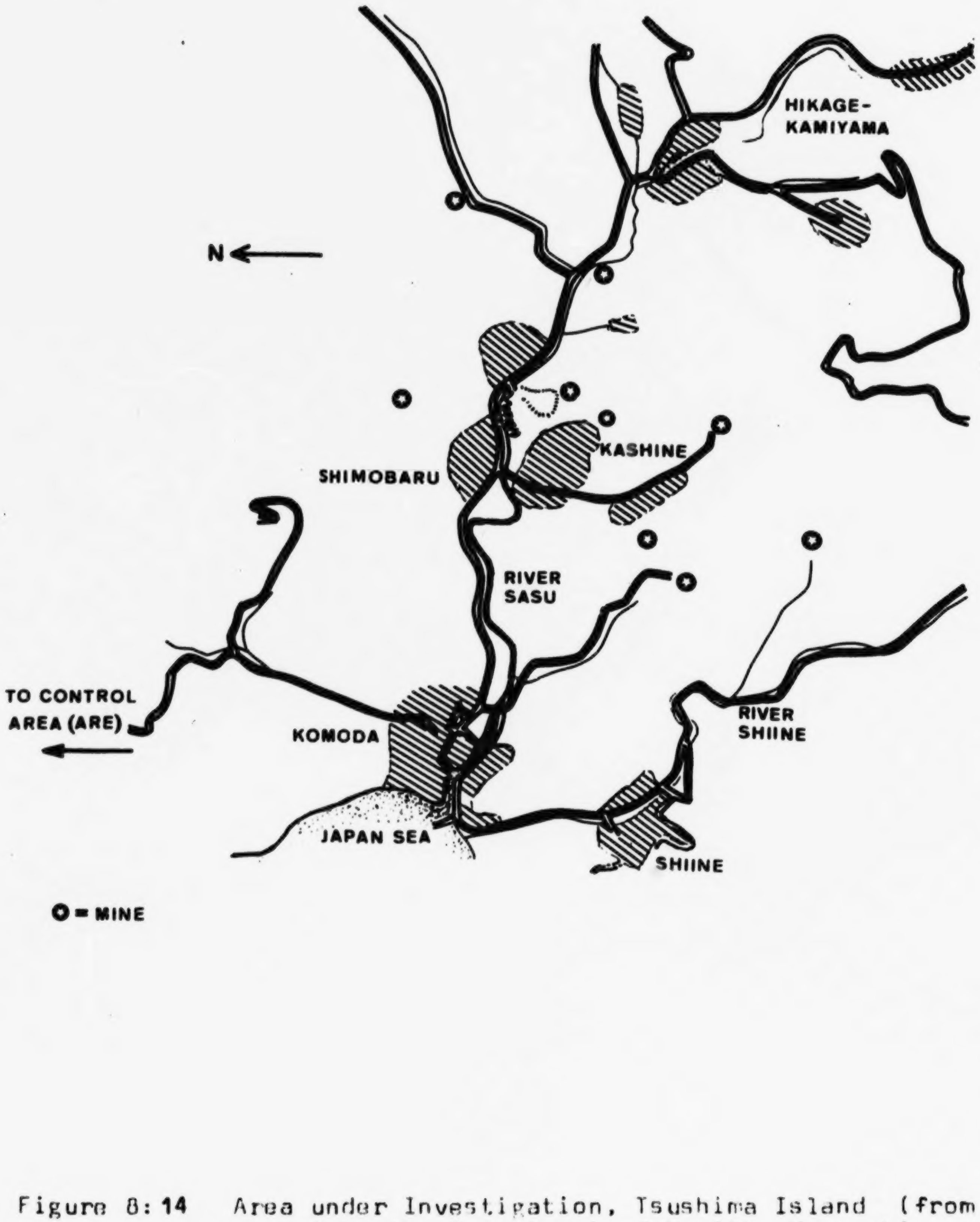
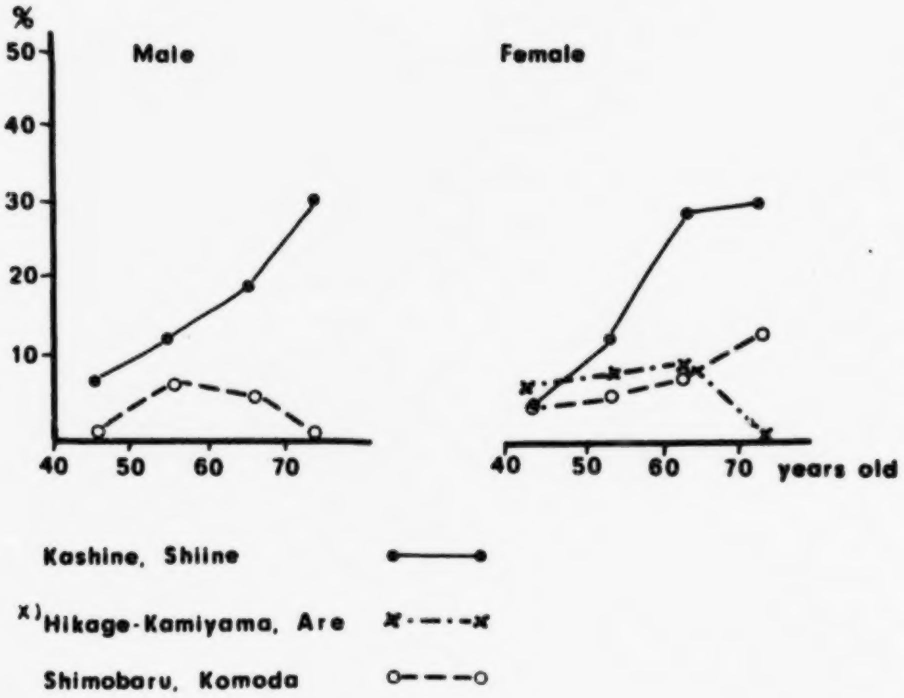
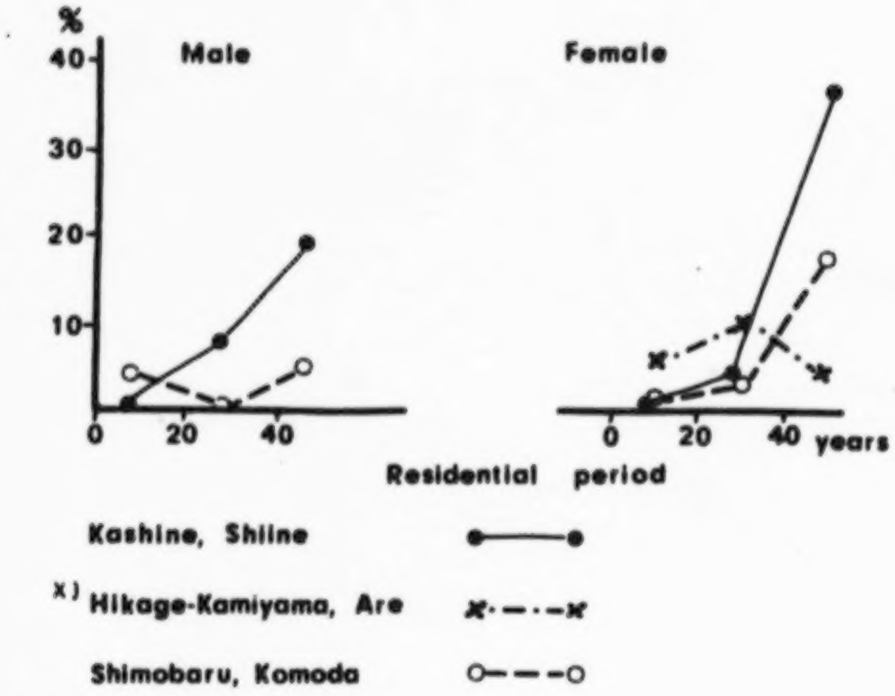

HIKAGE-
KAMIYAMA
N
KASHINE
SHIMOBARU
RIVER
SASU
TO CONTROL
AREA (ARE)
KOMODA
RIVER
SHIINE
JAPAN SEA
SHIINE
○ = MINE

Figure 8: 14 Area under Investigation, Tsushima Island (from report by the Department of Health, Nagasaki Prefecture, 1970).



x)No cases of proteinuria found among males

Figure 8:15 Prevalence of Proteinuria in Different Areas in Men and Women in Different Age Groups (from report by Department of Health, Nagasaki Prefecture, 1970).



x) No cases of proteinuria found among males

Figure 8:16 Prevalence of Proteinuria in Different Areas (Tsushima Island) in Men and Women in Relation to Time of Residence (from a report by the Department of Health, Nagasaki Prefecture, 1970).

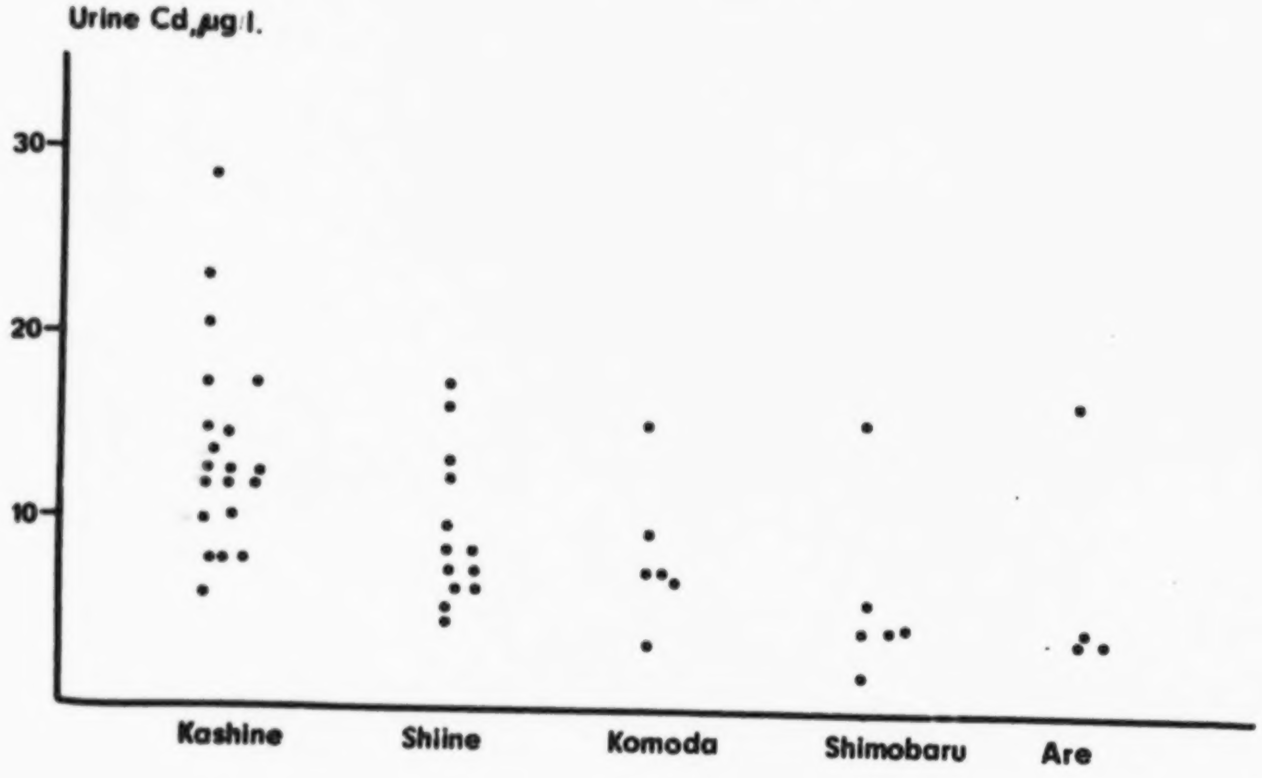


Figure 8:17 Urinary Cadmium Concentration of Subjects from Different Areas of Tsushima Island Positive for Urinary Protein and/or Glucose (from report by Department of Health, Nagasaki Precfecture, 1970).

NOT REPRODUCIBLE

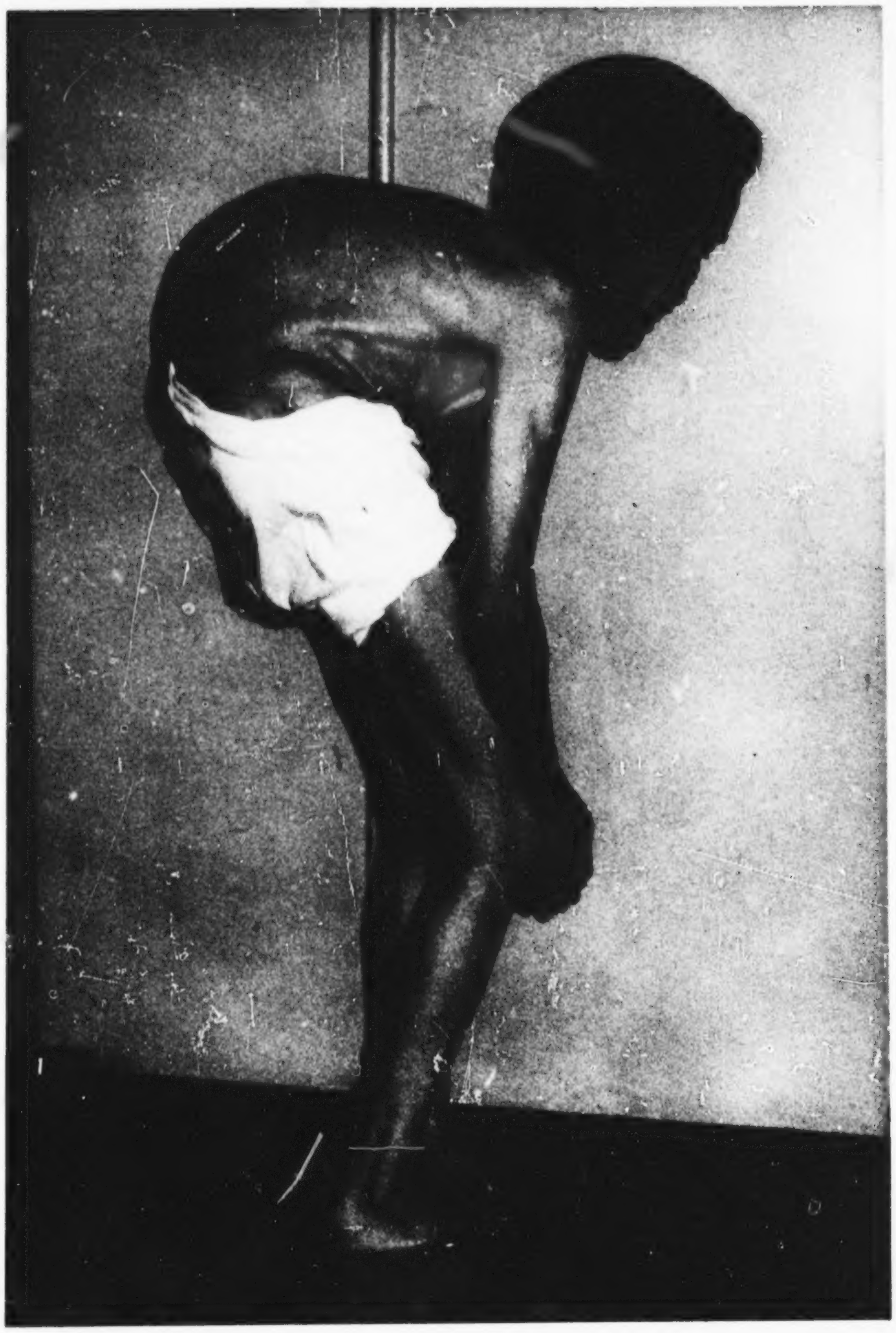


Figure 8:18 Advanced Skeletal Deformities in Itai-itai Patient (from Murata, personal communication).

NOT REPRODUCIBLE

Figure 8:19 Itai-itai Patient with Multiple Pseudofractures of the Ribs (from Murata, personal communication).

CHAPTER 9

GENERAL DISCUSSIONS AND CONCLUSIONS

NEED FOR FURTHER RESEARCH

In the preceeding chapters a detailed review of the different aspects of cadmium intoxication has been given. In each chapter whenever motivated there are special sections for conclusions drawn and these will not generally be repeated here. This chapter, instead, will deal with more general aspects on the problem, pointing out some of the most important conclusions and emphasizing the need for further studies.

Cadmium can undoubtedly constitute a most serious health problem. There is much evidence that exposure to this metal in the environment, both the industrial and the general environment, has given rise to serious intoxications in human beings. Such effects have been shown from inhaled as well as from ingested cadmium.

The manifestations of cadmium intoxication can take several forms. Inhalation of cadmium oxide fumes can produce acute damage in the lungs in the form of pneumonitis or pulmonary oedema. Prolonged exposure to dust or fumes can cause an invalidating emphysema.

Although dose-response relationships are generally uncertain, it was concluded (Chapter 5) that an exposure to about 500 min. mg/m^3 of cadmium oxide fumes is immediately dangerous from the point of view of acute pulmonary manifestations. Chronic exposure to cadmium oxide fumes, in concentrations well below 0.1 mg/m^3, is considered hazardous with reference to emphysema.

Systemic effects arise after absorption of cadmium. With the exposure that occurs from the general environment and also industrially, it is the effects due to long-term exposure to low concentrations of cadmium that are of interest. The critical organ is the kidney. Renal tubular dysfunction with proteinuria is a common manifestation. The renal tubular dysfunction may under certain circumstances give rise to severe secondary manifestations including a pronounced and invalidating osteomalacia. This form of cadmium intoxication has been seen industrially after inhalation of cadmium as well as after long-term ingestion of contaminated food. Other systemic effects include anemia and liver dysfunction.

In Japan the fully developed picture of cadmium intoxication with kidney damage and osteomalacia is known under the name "Itai-itai byo" (literally: ouch-ouch disease) because of the severe pains accompanying the skeletal disorder. A large number of cases of cadmium intoxication with renal dysfunction but without known osteomalacia are also reported from Japan. Contamination of the food, particularly rice, with cadmium is considered to be the main cause of this disorder. The contamination of the food has with all probability its primary cause in contaminated river water and in some places perhaps also in the contaminated ambient air. The reason why the manifestations of cadmium intoxication in Japan often have come to such an advanced stage is not quite clear. It may be that the exposure several years ago was very excessive, but there is also the possibility that poor nutritional habits, such as low intake of calcium, protein and Vitamin D have been essential to the problem.

In some animal experiments it has been possible to produce hypertension after prolonged exposure to cadmium. There is no conclusive evidence that cardiovascular disease in human beings is causally associated with cadmium exposure, although some statistical associations found in epidemiological studies merit further investigations.

Animal experiments have clearly shown that injections of cadmium salts cause malignancies. There are some data from human beings which tend to show an association between cadmium exposure and cancer. However, much more evidence is needed before any conclusions can be made concerning this causality.

The nature of the effects of cadmium on the cellular level has been discussed in several sections of the report and the intimate relationship between cadmium and zinc metabolism has been pointed out. There are mechanisms which are fairly well known, but much needs to be done until the complete picture of the different manifestations of cadmium intoxications are understood.

What makes cadmium contamination of the environment a particularly serious hazard is the pronounced tendency for cadmium to accumulate in the body. This is evident from autopsy data on human beings as well as from animal studies. Animal experiments show that the excretion of cadmium via urine and the gastrointestinal tract is extremely low, only a few percent of the absorbed amount. This in turn is reflected in a very long biological half-life of several hundred days. In human beings the excretion via urine has been shown to be very low, while data on gastrointestinal excretion are lacking.

Daily, human beings are exposed to a substantial amount of cadmium in food. Fortunately the absorption rate seems to be low. Some data on known accumulation of cadmium in the human body and estimated cadmium intake in the past, tend to show a retention of about 5 percent for human beings not excessively exposed to cadmium. Based on animal and human data, it is considered quite possible that under certain circumstances absorption in human beings may reach 10 percent (section 4.1.2.3).

The ambient air contains small amounts of cadmium and in the vicinity of certain factories the concentration can be considerable. High exposure is not uncommon in industries where cadmium is used. Absorption rate via inhalation is probably higher, than via ingestion. Depending on factors like particle size, absorption rates of 10-40 percent have been estimated (section 4.1.1.4). Also absorption via inhalation is subject to considerable uncertainty.

When absorbed, cadmium will accumulate in liver and kidneys. The larger the exposure, the more will be accumulated in the liver relative to other organs. Long-term exposure to fairly small amounts of cadmium will give kidney values corresponding to about one third of the total body burden. When kidney damage occurs, the concentration of cadmium in the kidneys will decrease substantially. This probably explains why advanced cases of cadmium intoxication, as seen in the Itai-itai disease and sometimes in industrial poisoning, will have low kidney levels in spite of high liver levels of cadmium.

When renal tubular dysfunction appears, the excretion of cadmium via the urine will increase drastically. Animal experiments have shown an increase of about 100 times. The fact that urinary cadmium excretion is virtually non-existent before renal dysfunction appears, makes the analysis of cadmium in urine useless as an indicator of total body burden. But if the purpose only is to detect cadmium induced renal dysfunction, it may be used, since increased cadmium excretion would point very strongly towards such an effect.

Cadmium levels in blood will increase with exposure. During exposure, though, it is not a good indicator of the body burden as blood levels also will reflect recent exposure to cadmium.

As was stated above, at long-term exposure to fairly low concentrations of cadmium, about one third of the cadmium will be found in the kidneys, Animal data as well as data from autopsies of workers with none or only a slight renal dysfunction, point towards 200 ppm (wet weight) of cadmium in the renal cortex as being the critical level for renal dysfunction, diagnosed through kidney function tests and occurrence of proteinuria. Based on this level and absorption and excretion data for cadmium, estimates have been made of exposures that are necessary to reach the critical concentration of cadmium in the kidneys. Table 6:2 gives examples of exposures and exposure times necessary to reach 200 ppm in the renal cortex. As can be seen from the table, a daily intake of about 100-150 μg of cadmium will result in about 200 ppm of cadmium in the renal cortex after 50 years of exposure with an absorption rate of 5 percent. Based on an absorption of 25 percent of inhaled cadmium, a mean concentration in the ambient air of about 1-1.5 $\mu g/m^3$ will give the same result. A worker exposed to cadmium industrially could expect to reach the critical level after an exposure to about 8 $\mu g/m^3$ after approximately 25 years of exposure. In these estimations simultaneous exposure via food and air has not been taken into account.

At birth, the human body only contains a total of about 1 µg of cadmium. At the age of about 50 years, a "normal" body burden of cadmium for an American "standard man" is about 30 mg. Concentrations in food and air, necessary to reach this body burden can be seen from data in table 6:3.

The following can be said concerning the needs for further research. There is an immediate and urgent need for research on the dose-response relationships. Above all, absorption and excretion rates should be further investigated. Such studies should include exposure via the peroral route as well as inhalation. Different cadmium compounds should be studied with reference to the influence of particle size at absorption via inhalation. The information on absorption to date is very inadequate and it goes without saying, that preventive measures, that need to be taken, may be quite different for different absorption rates. Animal experiments can certainly provide a substantial part of the necessary information. On human beings it should be possible to carry out metabolic studies where uptake and excretion of cadmium is examined over prolonged periods.

There is a need for more detailed studies on concentrations of cadmium relative to total body burden at different exposure levels in kidneys, but also in other organs.

A search for better indicators of cadmium levels in critical organs other than those of urine and blood concentrations should be pursued. Of special interest in this connection is hair.

The critical level in kidneys should be studied further. It should also be born in mind that effect levels used up until now have included only fairly gross effects. Dysfunctions may be found at considerably lower concentrations on a cellular level.

Epidemiological studies should be carried out on populations exposed in different degrees to cadmium. Such populations may be found within industries, but also in areas surrounding industries emitting cadmium. The unfortunate wide-scale contamination with cadmium in Japan may give unique possibilities for studies in that country on several aspects of dose-response relationships. When embarking on epidemiological studies due attention must be paid to methodological questions in order to make results from different studies comparable. Effects to be looked for should include renal dysfunction including proteinuria, certain cardiovascular diseases, and malignancies. The accumulation of cadmium in the body should be studied further in connection with autopsies in cases of accidental death as well as from other causes, particularly cancer and chronic renal, cardiovascular and pulmonary diseases.

High concentrations of cadmium have been found not only in the kidneys. The significance of an accumulation of cadmium in liver, pancreas and thyroid certainly merits further studies.

Virtually nothing is known about genetic and teratogenic effects of cadmium. There is a great need for studies in these areas.

Chelating agents found extensively in nature may have a deleterious effect in cadmium intoxication. There is an immediate need to examine the combined effects of cadmium and such agents (e.g. EDTA and NTA) in long-term studies.

It should be emphasized that there are severe gaps in the understanding of the mechanisms behind the different manifestations of cadmium intoxication. Much of our present knowledge of cadmium intoxication is based on studies on the metabolism of the metal. By stimulating further basic research on metal toxicology we can expect to get a better understanding of the complex effects of cadmium on human health.

Finally, it should be stressed that vast research needs exist concerning aspects of cadmium in the environment which indirectly are important for toxicological and epidemiological appraisals of cadmium. Although not directly within the scope of this review, it should be mentioned that there is a need for more data on the turnover of cadmium in nature, including the accumulation via air and water in food chains.

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